The Synthesis of Medium-Sized Rings and Macrocycles *via* a Cyclisation/Ring Expansion Cascade Reaction

Jack Wootton

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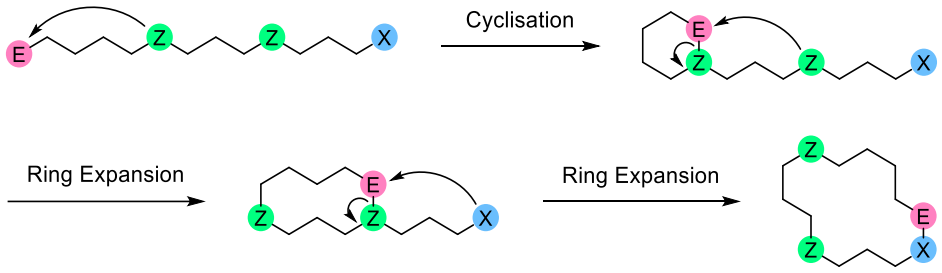
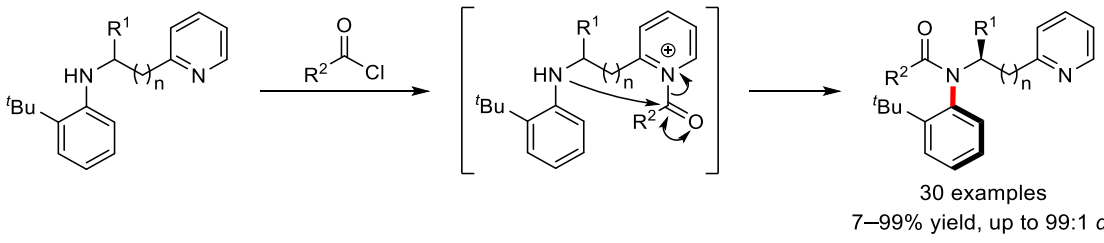
Abstract

The primary aim of this thesis was to expand the scope of the Cyclisation/Ring Expansion (CRE) cascade reaction, originally developed by the Unsworth group. CRE cascade reactions allow the synthesis of medium-sized rings and macrocycles without the need for high dilution conditions. In this thesis, the scope and limitations of this CRE cascade reaction using bis-electrophilic reagents were explored and in unsuccessful cases attempts were made to identify side products. The use of imines as internal nucleophiles was found to be unsuitable with clear side products forming that were quantified and characterised. Utilising multiple internal nucleophiles was also demonstrated, allowing the synthesis of larger ring systems (up to 18-membered). Control reactions were performed for one of these substrates containing two internal nucleophiles, and clearly highlighted the importance of the internal nucleophiles, providing strong evidence for the proposed CRE cascade mechanism.



This thesis also presents a new method for the diastereoselective synthesis of atropisomeric anilides based on an intramolecular acyl transfer *via* a tethered pyridyl moiety. This method was shown to have a broad scope, gave anilides in high *dr* (up to 99:1) and typically gave products in high yields, which were isolated as single diastereoisomers. Control reactions provided strong evidence for the proposed acyl transfer mechanism and DFT studies provided insights on the transition states for the acyl transfer reaction to justify the observed selectivity. Thermal epimerisation experiments allowed access to both diastereoisomers and demonstrated the stability of the C–N chiral axis ($t_{1/2}$ = >1000 years at 25 °C).



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Author Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is a presentation of original work. The research presented in this Thesis was carried out at the University of York between October 2021 and February 2025. This work has not previously been presented for a degree or other qualification at this University or elsewhere. All sources are acknowledged as references.

Jack M. Wootton

Abbreviations

Ac	acetyl
AIBN	2,2′-azobis(2-methylpropionitrile)
APCI	atmospheric pressure chemical ionisation
aq.	aqueous
Ar	aromatic
ATR	attenuated total reflectance
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
BJ	Becke-Johnson
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bpin	pinacolborane
Bu	butyl
ca.	circa
calcd.	calculated
CARE	Conjugate Addition/Ring Expansion
cat.	catalytic
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CRE	Cyclisation/Ring Expansion
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
$(DHQ)_2PYR$	hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether

DIBAL-H	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAc	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
dt	doublet of triplets
EDC	*N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
FDA	Food and Drug Administration
Fmoc	9-fluorenylmethyloxycarbonyl
GABA	γ-aminobutyric acid
h	hours
HFIP	hexafluoroisopropanol
HIRE	Hydrated Imidazoline Ring Expansion
HMBC	heteronuclear multiple bond correlation
HOBt	1-hydroxybenzotriazole
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
IR	infrared
IRC	intrinsic reaction coordinate
IUPAC	international union of pure and applied chemistry
LDA	lithium diisopropylamide
LED	light-emitting diode
LiHMDS	lithium hexamethyldisilazane

m	multiplet
m-	meta
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Mes	mesityl
MMFF	molecular mechanics force field
m.p.	melting point
Ms	mesyl
NaHMDS	sodium hexamethyldisilazane
NMDAR	*N*-methyl-D-aspartate receptor
NMP	1-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o-	ortho
ODRE	Oxidative Dearomatisation-Ring-Expanding Rearomatisation
p	pentet
p-	para
Ph	phenyl
PIFA	[bis(trifluoroacetoxy)iodo]benzene
Piv	pivaloyl
PMB	*para*-methoxybenzene
ppm	parts per million
Pr	propyl
q	quartet
R_f	retention factor
RT	room temperature
s	singlet
sat.	saturated
SCF	self-consistent field
SEGPHOS	5,5’-bis(diphenylphosphino)-4,4’-bi-1,3-benzodioxole
SET	single electron transfer
SMD	solvation model based on density
S_NAr	nucleophilic aromatic substitution

SPS	solvent purification system
STAB	sodium triacetoxyborohydride
SuRE	Successive Ring Expansion
t	triplet
T3P	propylphosphonic anhydride
TBAF	tetrabutylammonium fluoride
td	triplet of doublets
Temp.	temperature
Tf	triflate
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time of flight
Ts	tosyl
TSA	toluenesulfonic acid
tt	triplet of triplets
UATR	universal attenuated total reflectance
UV	ultraviolet
XRD	X-ray diffraction
µw	microwave

1 Introduction

1.1 Macrocyclisation

Medium-sized rings (8–11 membered) and macrocycles (12+ membered) are a versatile class of compounds with a range of different uses (Figure 1); for example, in molecular sensing,[1,2] catalysis[3,4] and supramolecular chemistry.[5,6] They are also found in many natural products and have applications in medicinal chemistry,[7,8] although notably, naturally derived macrocycles (*e.g.* macrolides) and cyclic peptides tend to dominate in the area of macrocyclic medicinal chemistry,[9] mainly due to the synthetic challenges associated with the synthesis of 8+ membered ring systems. These challenges include the loss of entropy upon cyclisation and destabilizing transannular interactions in the cyclised product, both of which can provide a barrier to cyclisation. Transannular interactions are often especially problematic in medium-sized rings, which results in these systems often being the most challenging ring sizes to synthesise.[10]

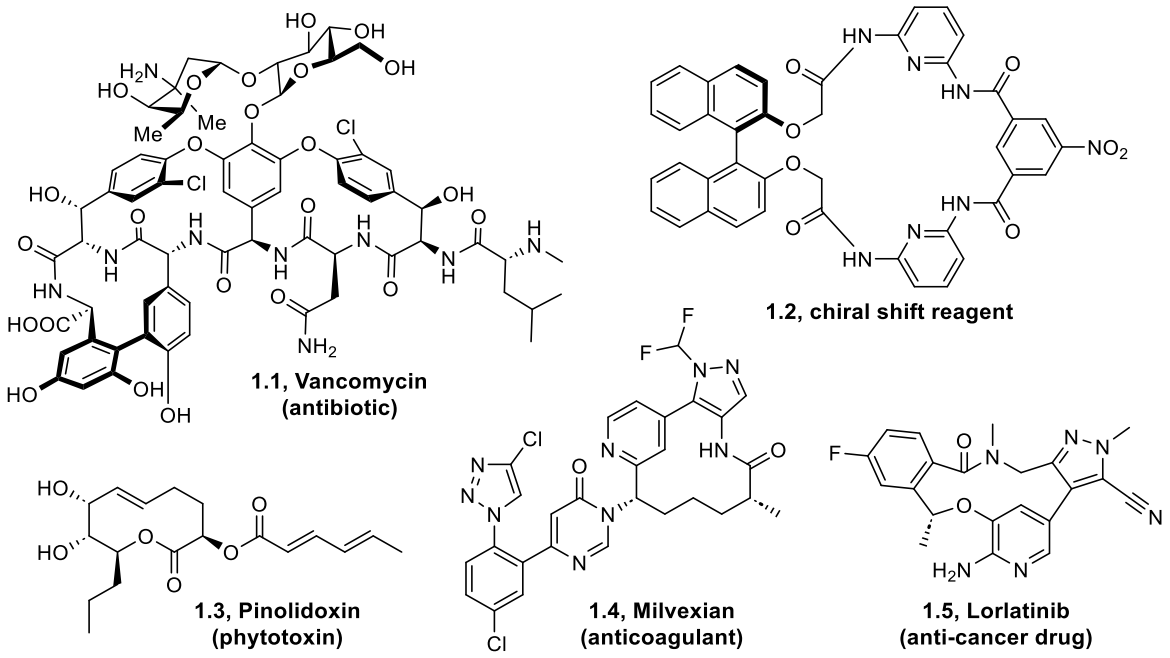


Figure 1. Examples of medium-sized rings/macrocycles.

Classical approaches to macrocyclisation involve the direct end-to-end cyclisation of a linear precursor. However, dimerisation is a common side reaction in these types of cyclisations (Figure 2). The most widely used strategy to minimize side reactions is the high-dilution approach[11] as this reduces the likelihood of two molecules colliding and hence reduces the rate of the intermolecular dimerisation reaction, while having minimal impact

on the rate of the intramolecular cyclisation. This approach has downfalls however: the large solvent volumes required are impractical when scaling up reactions due to handling problems, and there are economic and environmental disadvantages associated with reagent/solvent costs and increased waste.[12] Efforts have therefore been focused on creating alternatives to high-dilution and these include, pseudo-high-dilution,[13,14] phase separation strategies[15] and methods for preorganization of the linear precursor based on templation or conformational control.[16]

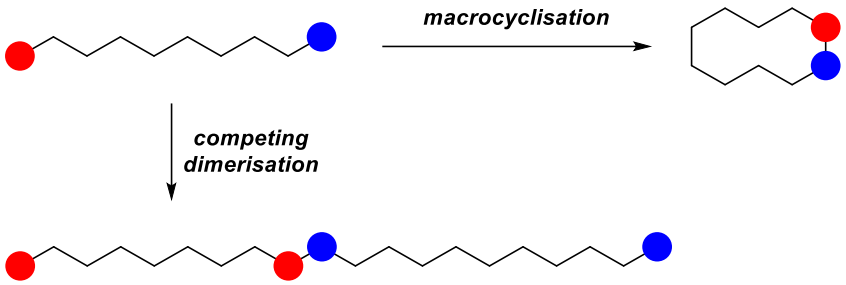


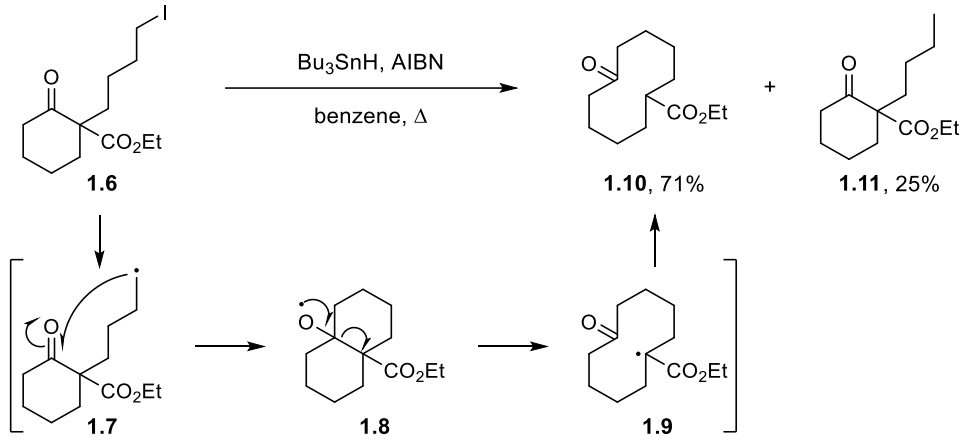
Figure 2. Macrocyclisation vs dimerisation.

Alternatively, direct end-to-end cyclisation can be avoided completely by using ring expansion strategies. These strategies revolve around 'growing' larger ring systems from smaller starting materials *via* rearrangement reactions. Typically, ring expansion strategies rely on the formation of a bicyclic scaffold which can undergo some type of cleavage of the bridging bond which results in the overall expansion of the ring size. Ring expansion reactions can be broadly grouped into three different categories: radical-based, pericyclic and fragmentation-based ring expansion. Each of these will be discussed in turn below.

1.2 Radical Ring Expansion

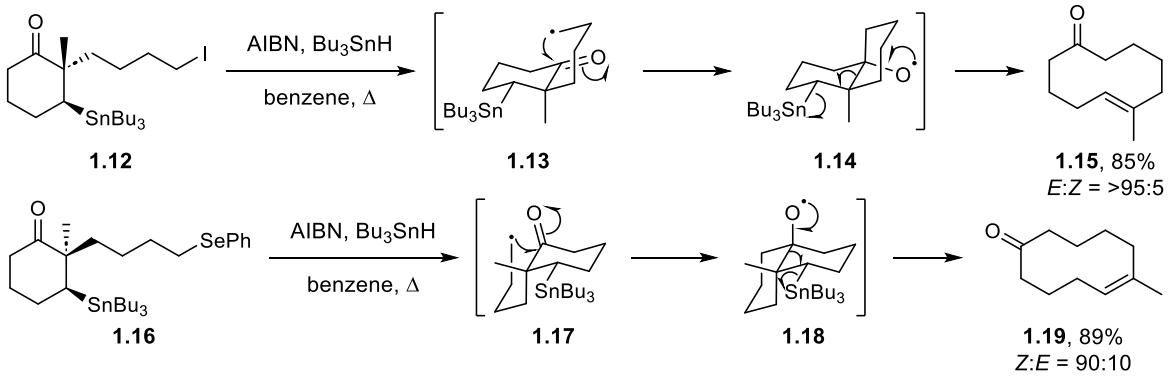
Radical ring expansion reactions involve the generation of a radical species which then undergoes a fragmentation/rearrangement, often driven by an increase in radical stability, to yield a ring expanded product. This is exemplified in the work of Dowd and co-workers who reported the radical ring expansion of β-keto esters (Scheme 1).[17] Alkyl iodide **1.6** is reacted with AIBN and tributyltin hydride to generate primary alkyl radical **1.7**. This radical then attacks the ketone group forming bicyclic oxygen centred radical **1.8**, which undergoes fragmentation to give tertiary radical **1.9**. Radical **1.9** being a tertiary radical and conjugated with an ester group means this radical species is more stabilised, relative to the starting radical **1.7**, providing the driving force for ring expansion in this reaction. Direct

reduction of the alkyl iodide **1.6** was found to be a competing process, with the reduced product **1.11** isolated as a minor side product.



Scheme 1. Dowd-Beckwith radical ring expansion of cyclic β-keto esters.

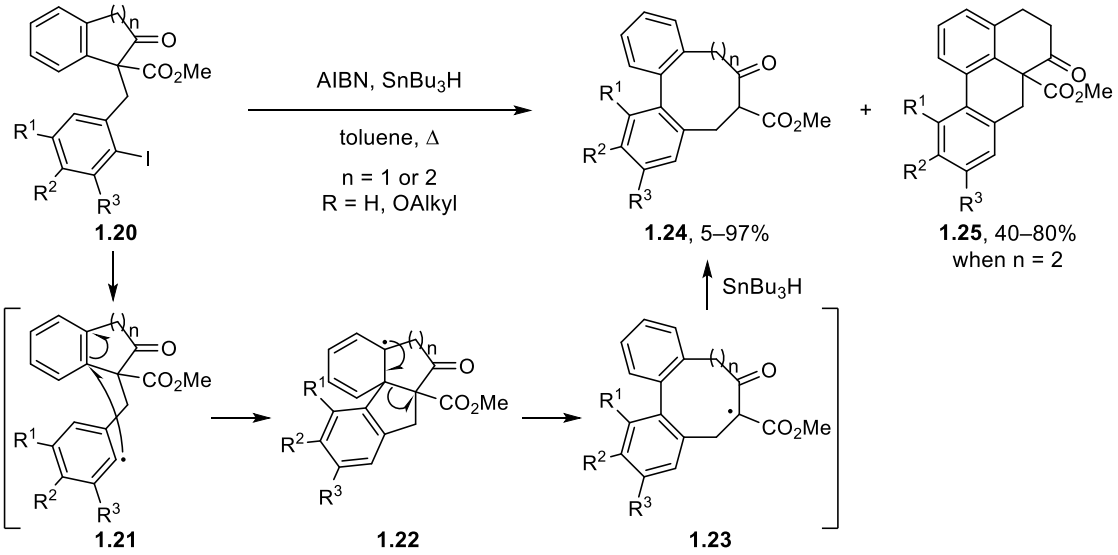
Baldwin and co-workers reported a similar radical based ring expansion (Scheme 2).[18] In this reaction, primary alkyl radicals are generated from iodides (**1.12**) or selenides (**1.16**) with AIBN and tributyltin hydride. Attack of this radical into the ketone group (**1.13** → **1.14**) gives a bicyclic intermediate which then undergoes a fragmentation, eliminating a more stable tributyltin radical and generating the 10-membered cyclic alkene products. The alkene geometry can be controlled by the stereochemistry of the precursor, when using a *cis*-starting material (**1.12**) the *E*-alkene (**1.15**) forms preferentially, whilst the *trans*-starting material (**1.16**) gives the *Z*-isomer (**1.19**). This is a result of the bulky tributyltin group orientating itself in the less hindered equatorial position of the *cis*-decalin intermediate.



Scheme 2. Radical ring expansion with elimination to form cyclic alkenes.

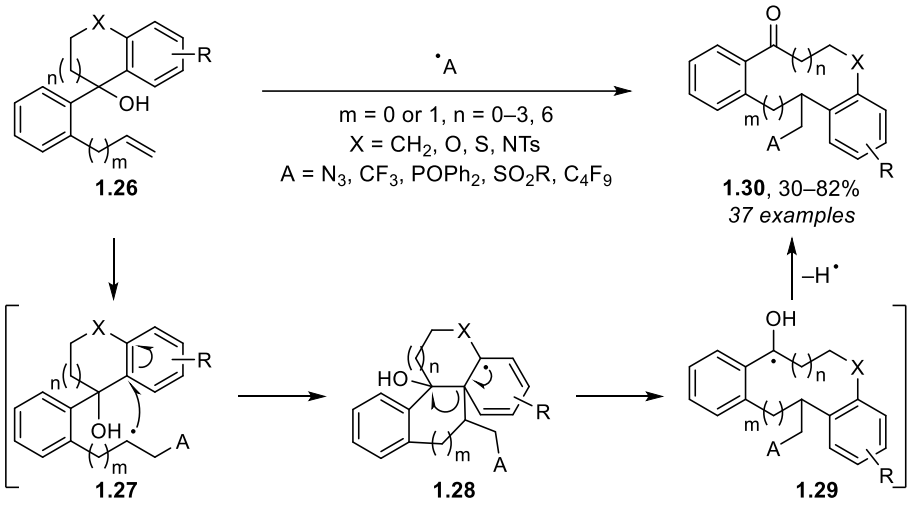
It is also possible to use aryl radicals in ring expansion reactions, as demonstrated by Harrowven and co-workers in an *ipso*- substitution reaction (Scheme 3).[19] The aryl radical **1.21** was generated from an aryl iodide **1.20**. In this case the radical attacks into the aromatic system, rather than the carbonyl, forming bicyclic intermediate **1.22**.

Fragmentation of this intermediate causes rearomatisation and gives radical **1.23**, which is stabilised by conjugation with the ketone and ester groups. A final hydrogen abstraction gives the medium-sized ring products **1.24** in 5–97% yield. The reaction worked well for the indanone series (n = 1) with only the desired product being isolated. However, the tetralone series (n = 2) was more challenging and resulted in a competing *ortho*- cyclisation pathway giving side products **1.25**. This was rationalised by the *ortho*- attack transition state in the indanone series be significantly higher in energy than in the tetralone series.



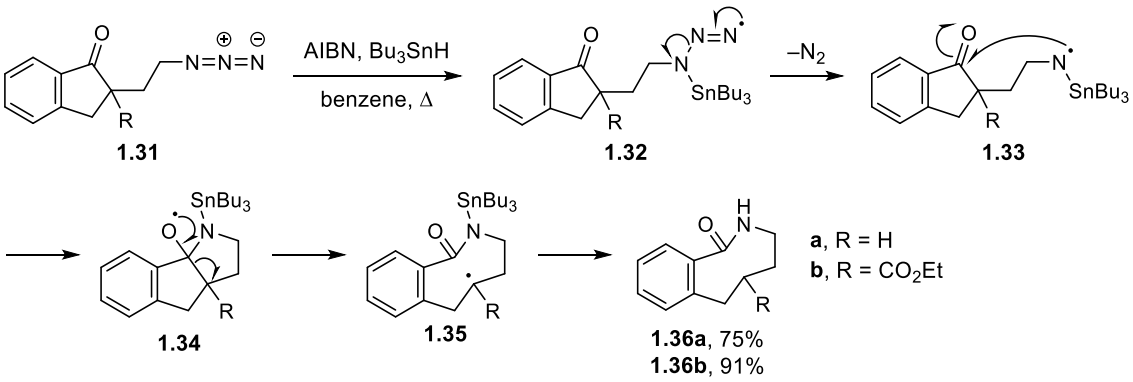
Scheme 3. Aryl radical ring expansion to form medium-sized cyclic β-keto esters.

In related work, Liu and co-workers reported an *ipso*- substitution reaction using sp^3 radicals, generated by the reaction of an electrophilic radical species (A) with an alkene **1.26** (Scheme 4).[20] Azide, phosphonyl, sulfonyl and perfluoroalkyl radicals were all found to be suitable for this transformation, although each required slightly different reaction conditions to obtain the optimum yields, due to the different methods of generating the initial radical species. Following generation of the radical (A), addition to the alkene **1.26** took place to give intermediate radical **1.27** which could attack into the aromatic system forming bicyclic intermediate **1.28**. Rearomatisation and fragmentation of this intermediate gave ketyl radical **1.29** which upon loss of a hydrogen radical gave the desired products **1.30**. Using this method a diverse range of products was able to be generated with ring sizes from 9–14-membered and various synthetic handles which allowed further functionalisation of the products.



Scheme 4. Radical addition and *ipso*- substitution to give medium-sized or macrocyclic ketones.

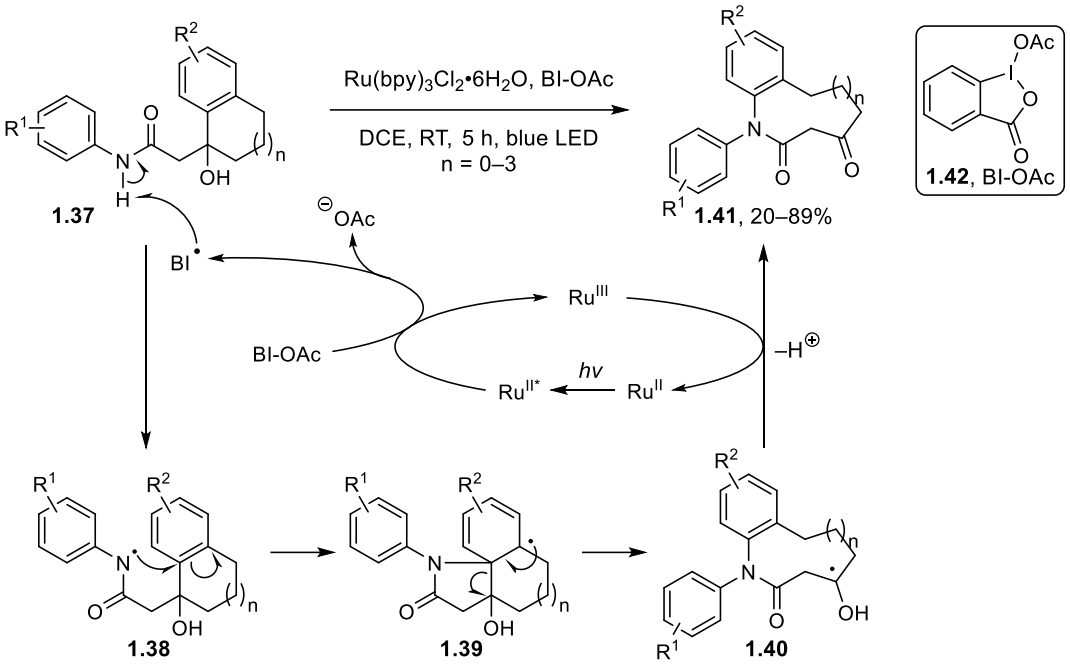
Kim and co-workers reported a ring expansion based on a nitrogen centred radical (Scheme 5).[21] Azide **1.31** was reacted with AIBN and tributyltin hydride to generate radical **1.32**, which undergoes a fragmentation to give aminyl radical **1.33** and releases nitrogen gas. This aminyl radical then attacks into the ketone forming bicycle **1.34** which fragments to form medium-sized ring **1.35**. Hydrogen abstraction furnished the final products in 48–96% yields. Whilst the presence of an ester group (**1.36b**) gave increased yields, presumably due to the stabilising effect on the radical intermediate, the reaction could proceed with a simple hydrogen (**1.36a**) or alkyl group in this position.



Scheme 5. Nitrogen centred radical ring expansion to form medium-sized lactams.

Amidyl radicals can also be used, as was the case in a photocatalytic ring expansion reported by Liu and co-workers (Scheme 6).[22] Using a blue LED, a ruthenium catalyst was promoted to an excited state, from which the iodine(III) reagent **1.42** could be reduced to a radical species. Hydrogen abstraction then gave the desired amidyl radical **1.38** which underwent cyclisation and fragmentation (**1.38** → **1.39** → **1.40**) to give ketyl radical **1.40**. Single-electron oxidation of the ketyl radical, by the Ru^{III} species generated at the start of

the reaction, furnished the desired medium-sized rings **1.41** and regenerated the Ru^{II} photocatalyst. Using this method, products spanning the whole medium-sized ring range could be accessed (8–11-membered), although electron donating groups on the anilide were not tolerated, which the authors ascribed to oxidative decomposition.

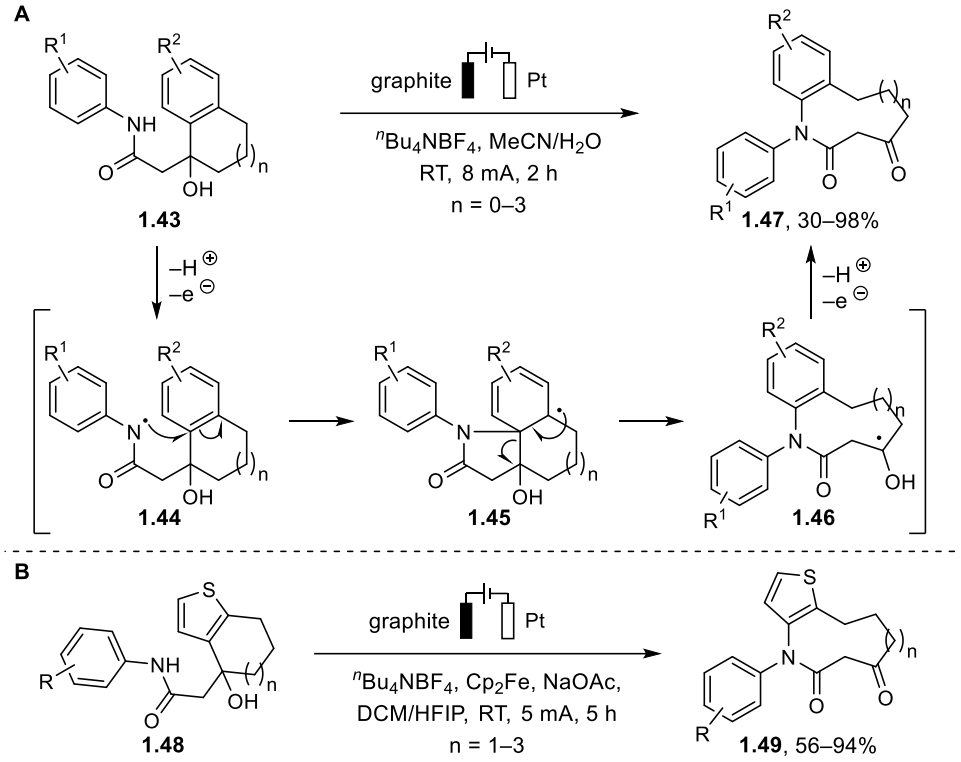


Scheme 6. Photocatalytic generation of amidyl radicals that undergo ring expansion.

Radicals can also be generated by electrochemical means, as demonstrated by Ruan and co-workers (Scheme 7A).[23] By using an undivided electrochemical cell with a graphite anode and platinum cathode the N–H bond of amide **1.43** could be oxidised at the anode to give nitrogen centred radical **1.44**. This then undergoes cyclisation on the *ipso*- position of the aromatic ring followed by fragmentation (**1.44** → **1.45** → **1.46**) to give ketyl radical **1.46**, which then undergoes single electron oxidation and proton loss to give medium-sized lactams **1.47**. Interestingly, no attack at the *ortho*- position was observed and DFT calculations showed that attack at this position proceeded through a higher energy transition state and so was unfavourable. This method represents a greener procedure for radical generation, not requiring the use of toxic reagents that are typically used as radical initiators or the use of costly precious metals.

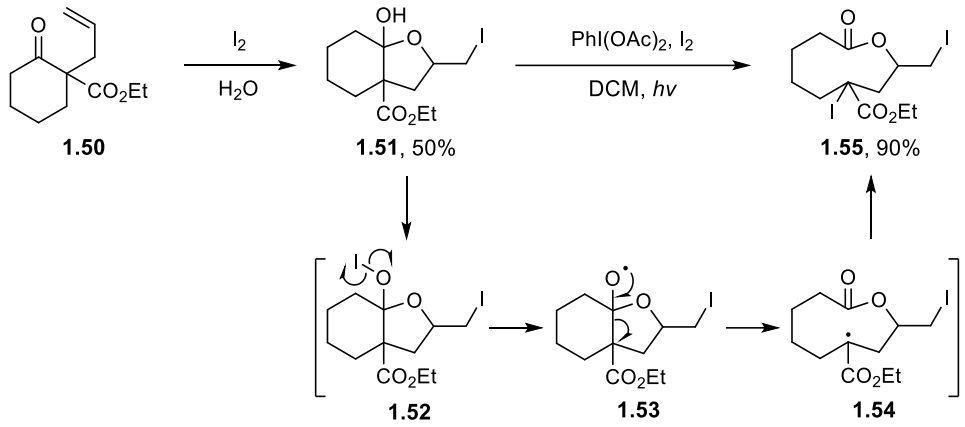
At the same time, Lei and co-workers reported the same concept using slightly different reaction conditions (Scheme 7B).[24] With these modified conditions they were able to tolerate thiophene containing precursors such as **1.48** and strongly electron donating

groups which proved challenging in previous work. The authors found that catalytic amounts of ferrocene were beneficial for the reaction, which they postulated was due to the oxidised ferrocene being able to oxidise the final ketyl radical intermediate to the product, as well as possibly preventing over oxidation of the products.



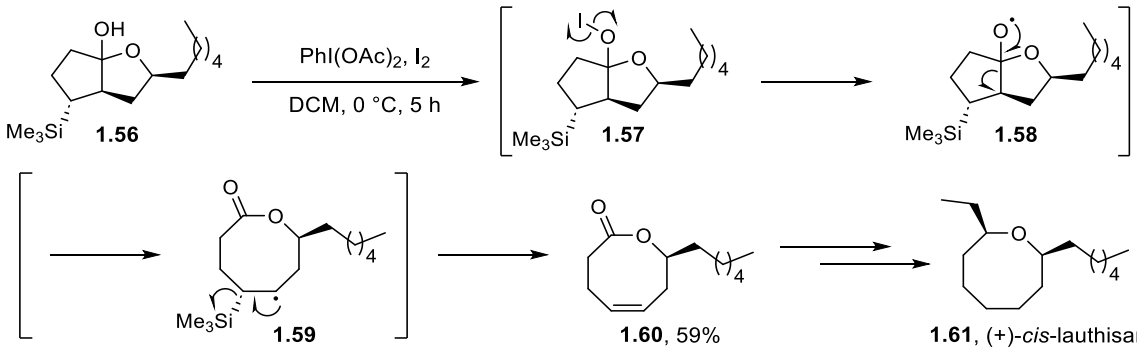
Scheme 7. Ring expansion using electrochemically generated radicals.

Oxygen centred radicals can also undergo ring expansion reactions, as was described by Hassner and co-workers in a photochemically initiated radical fragmentation (Scheme 8).[25] Lactol **1.51** was prepared by the reaction of alkene **1.50** with iodine and water. Radical initiation was carried out using (diacetoxyiodo)benzene under light irradiation to generate the alkoxy radical **1.53**. This then fragments into carbon centred radical **1.54** containing an ester group which stabilises this radical and helps drive the reaction forward. Finally trapping of the radical **1.54** with an iodine radical gave the desired product **1.55** in high yield.



Scheme 8. Photoinduced radical fragmentation of alkoxy radicals for the synthesis of lactones.

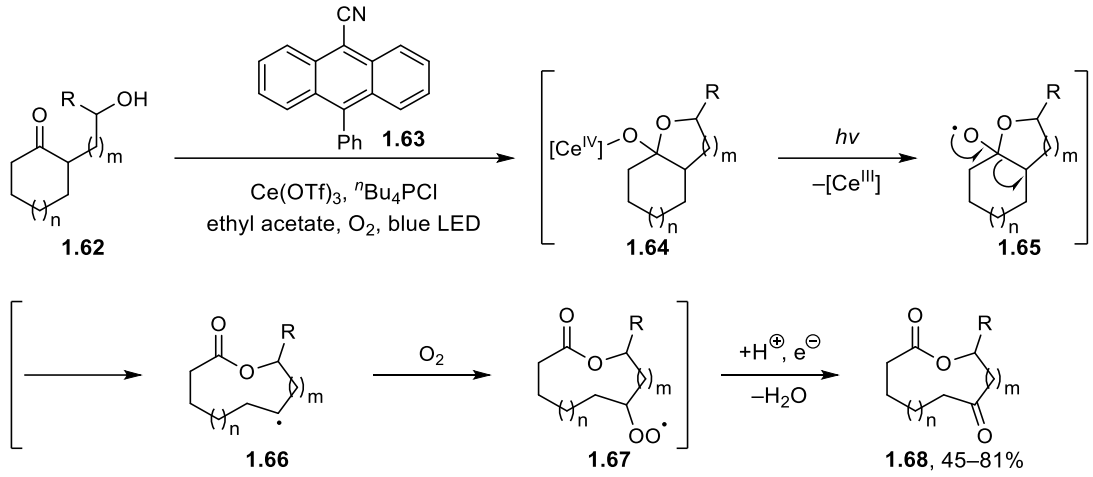
Posner and co-workers developed an alkoxy radical ring expansion without the need for an ester group (Scheme 9).[26] Instead, following generation and fragmentation of the alkoxy radical (**1.56** → **1.57** → **1.58** → **1.59**), an elimination can occur with a strategically placed trimethylsilyl group to give alkene **1.60**. The authors proposed a non-concerted mechanism for the fragmentation and elimination on the basis that only the *cis*-alkene was formed in the reaction, rather than the *trans*-alkene that would result from a concerted mechanism. Using this method, they were able to synthesis the natural product (+)-*cis*-lauthisan as a single enantiomer in only six steps.



Scheme 9. Alkoxy radical fragmentation and elimination that was successfully applied to the synthesis of (+)-*cis*-lauthisan.

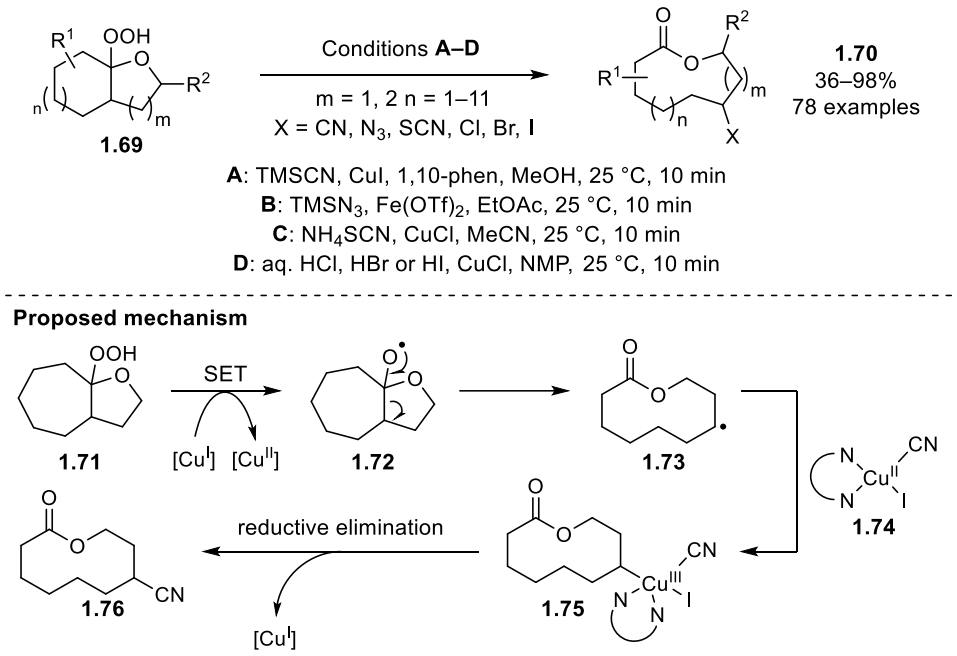
Zuo and co-workers reported a cerium mediated photocatalytic reaction of lactols (Scheme 10).[27] Complexation of cerium with hydroxy ketones **1.62** pushed the equilibrium to the lactol form, following which the cerium(III) was oxidised to cerium(IV) (**1.64**) by the action of the anthracene co-catalyst **1.63**. This cerium(IV) complex was photoexcited giving oxygen centred radical **1.65**, which could fragment into carbon centred radical **1.66**. This was then trapped by molecular oxygen giving peroxyl radical **1.67**, which was subsequently

reduced to the ketone **1.68** by photoexcited anthracene **1.63**. This 3/4-atom ring expansion showed good functional group tolerance and allowed a diverse range of medium-sized rings and macrocycles to be made, ranging from 9–19-membered rings.



Scheme 10. Photoinduced cerium catalysed ring expansion of hydroxy ketones.

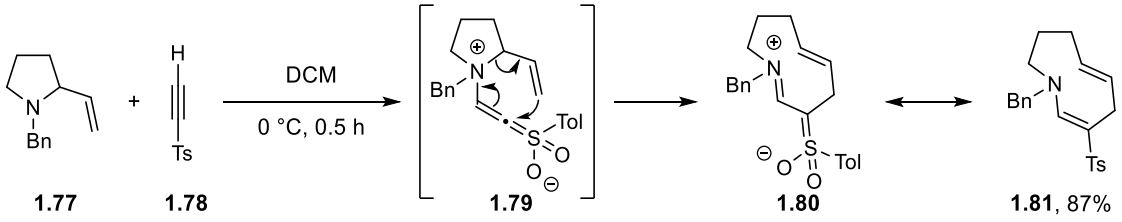
A similar reaction was reported by Guo and co-workers, in this case starting from a hemiketal hydroperoxide **1.69** which could be isolated or generated *in situ* (Scheme 11).[28] An impressive 78 examples with ring sizes ranging from 9–19-membered were synthesised by this Cu/Fe catalysed ring expansion, with the ability to install six different functionalities: nitrile, azide, thiocyanate, chloride, bromide and iodide. Single electron transfer between a Cu(I) species and hydroperoxide **1.71** produces alkoxy radical **1.72** that undergoes β-scission to give carbon centred radical **1.73**. This can be trapped by Cu(II) species **1.74** giving the unusual Cu(III) species **1.75**. Reductive elimination then gave the functionalised medium-sized ring **1.76**.



Scheme 11. Cu/Fe catalysed radical ring expansion of hemiketal hydroperoxides to give functionalised medium-sized rings and macrocycles.

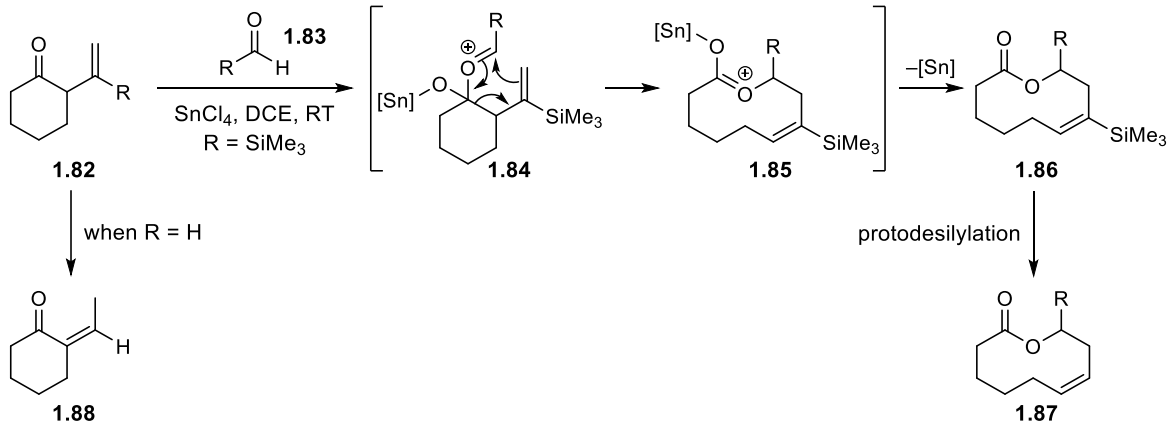
1.3 Pericyclic Ring Expansion

Pericyclic reactions are concerted reactions featuring a cyclic flow of electrons *via* a single transition state. These reactions can involve the cleavage of single bonds, and if this occurs with an appropriately designed substrate, medium-sized rings and macrocycles can be synthesised. Back and co-workers used a 3-aza-Cope rearrangement to synthesise 9–11-membered medium-sized rings and one 17-membered macrocycle (Scheme 12).[29] To do this, they reacted tertiary cyclic amine **1.77** with alkyne **1.78** in a conjugate addition reaction to give zwitterion **1.79**. This intermediate can then undergo a 3-aza-Cope rearrangement to give the medium-sized ring **1.80**/**1.81**. By using a tertiary amine precursor, they were able to carry out this reaction under very mild conditions, that are atypical of aza-Cope rearrangements, due to the neutralisation of charge providing a driving force for this reaction.



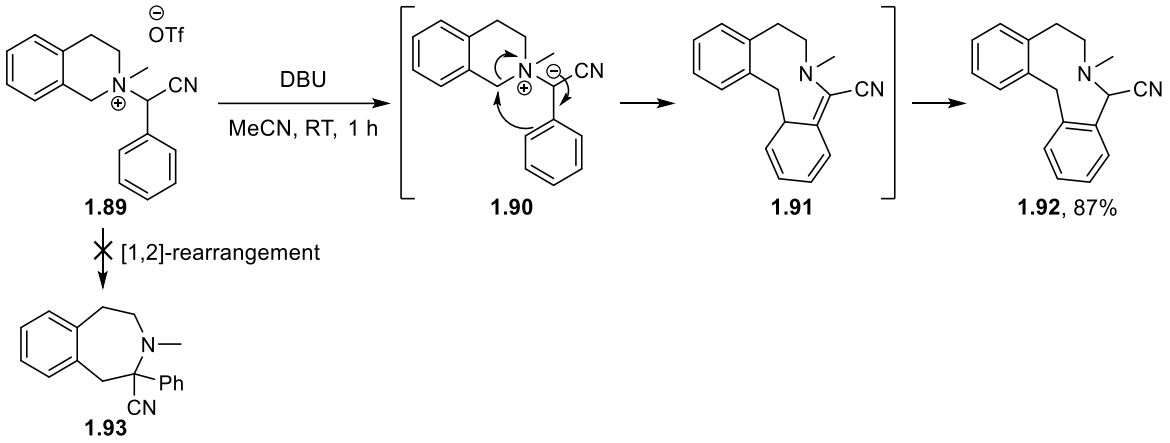
Scheme 12. Conjugate addition and 3-aza-Cope rearrangement in the synthesis of medium-sized rings.

Goeke and co-workers used a Lewis acid catalysed oxy-Cope rearrangement to synthesise 10-membered lactones (Scheme 13).[30] Ketone **1.82** was reacted with an aldehyde **1.83** in the presence of tin chloride, which acts as a Lewis acid leading to the formation of intermediate **1.84**. This then undergoes rearrangement to medium-sized ring **1.85** which, following dissociation of the tin catalyst, gives the desired lactones **1.86** predominantly as the *E*-alkene. Previous work by the same group found that monosubstituted alkenes (R = H) typically undergo isomerisation to the more thermodynamically stable alkene **1.88**, rather than undergoing the desired rearrangement.[31] The use of a trimethylsilyl (TMS) group prevented this isomerisation by increasing the rate of rearrangement, and following this could be removed by protodesilylation to give disubstituted alkene products **1.87**.



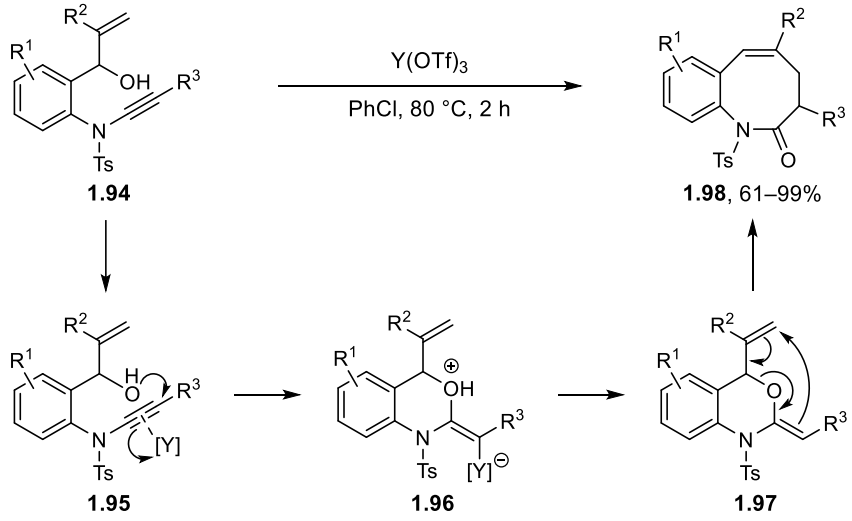
Scheme 13. Lewis acid catalysed oxy-Cope rearrangement.

Opatz and co-workers reported the serendipitous discovery of a [1,4]-sigmatropic rearrangement which was used to synthesise a range of 9-membered rings (Scheme 14).[32] Ammonium triflate **1.89** was reacted with a base with the expected product **1.93** being the result off a [1,2]-Stevens rearrangement. However, this did not occur, instead following deprotonation to form ylide **1.90**, a [1,4]-sigmatropic rearrangement took place forming 9-membered ring **1.91** which rearomatises to give the isolated product **1.92**.



Scheme 14. [1,4]-sigmatropic rearrangement to form 9-membered rings.

Claisen rearrangements have also been utilised in ring expansion as Ye and co-workers demonstrated in the synthesis of medium-sized lactams (Scheme 15).[33] Ynamides **1.94** were reacted with an yttrium triflate catalyst which coordinated to the alkyne to give intermediate **1.95**. This facilitated attack of the alcohol into the alkyne to form vinyl-yttrium intermediate **1.96**. Proton transfer gives bis-alkene **1.97**, which is setup to undergo a Claisen rearrangement, driven by the formation of the more stable amide functionality, to form lactam **1.98**.

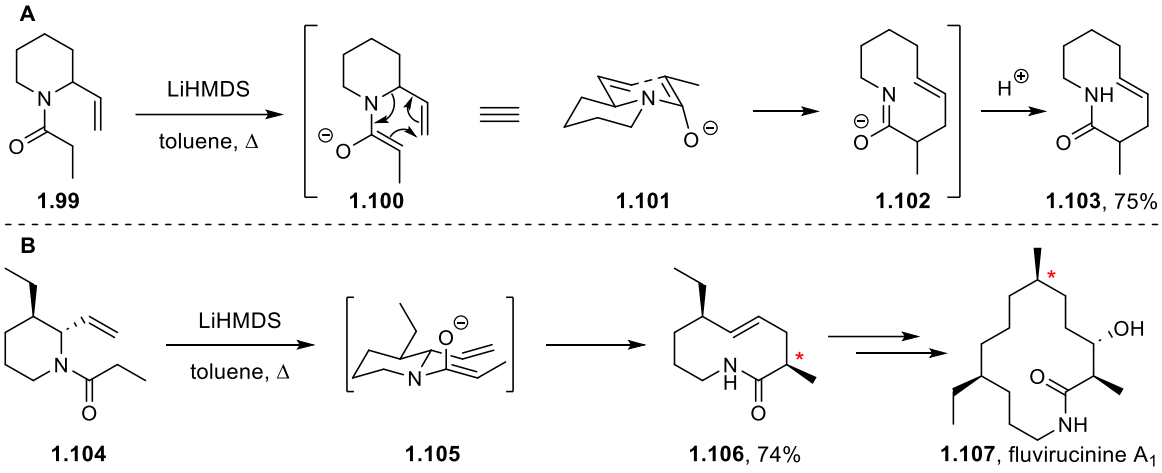


Scheme 15. Hydroalkoxylation and Claisen rearrangement cascade giving medium-sized rings.

Suh and co-workers used an aza-Claisen reaction to synthesise 10-membered lactams (Scheme 16A).[34] Reacting amide **1.99** with LiHMDS gave the enolate **1.100** which underwent an aza-Claisen rearrangement to give ring expanded product **1.102**. Protonation by the addition of water yielded the desired lactam **1.103** exclusively with *E*-alkene

geometry. This was rationalised by the chair-chair-like transition state **1.101** and the formation of the *Z*-enolate.

The same group also applied this method to the stereoselective synthesis of the natural product fluvirucinine A_1 (Scheme 16B).[35] An enantiopure sample of amide **1.104** was reacted with LiHMDS to give enolate **1.105** which underwent aza-Claisen rearrangement to give lactam **1.106** as a single diastereoisomer. The stereochemical outcome was rationalised by the formation of chair-chair-like transition state, with all substituents in more favourable equatorial positions, and the formation of the more favourable *Z*-enolate. Using this method, they were able to install a key stereogenic centre (*) that allowed the synthesis of enantiopure fluvirucinine A_1.

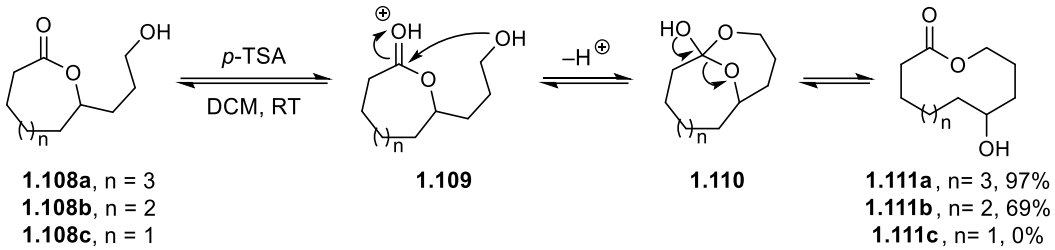


Scheme 16. [A] aza-Claisen rearrangement in the synthesis of medium-sized lactams. [B] Application to the stereoselective synthesis of fluvirucinine A_1.

1.4 Fragmentation Ring Expansion

Fragmentation ring expansion is the largest class of ring expansion reactions and involves the generation of a bicyclic precursor which can undergo fragmentation *via* two-electron processes to give ring expanded products. An early example of a fragmentation ring expansion is a translactonisation reported by Corey and co-workers (Scheme 17).[36] 9-Membered lactone **1.108a**, with a pendant alcohol, underwent translactonisation in acidic conditions *via* the bicyclic intermediate **1.110**, which fragments into the larger 12-membered lactone **1.111a**. Since all steps in this reaction are reversible, the thermodynamically most favourable product is formed, which in this case is the 12-membered lactone **1.111a**. The outcome of the reaction therefore provides information about the relative stability of different ring sizes. The reaction of 8-membered lactone

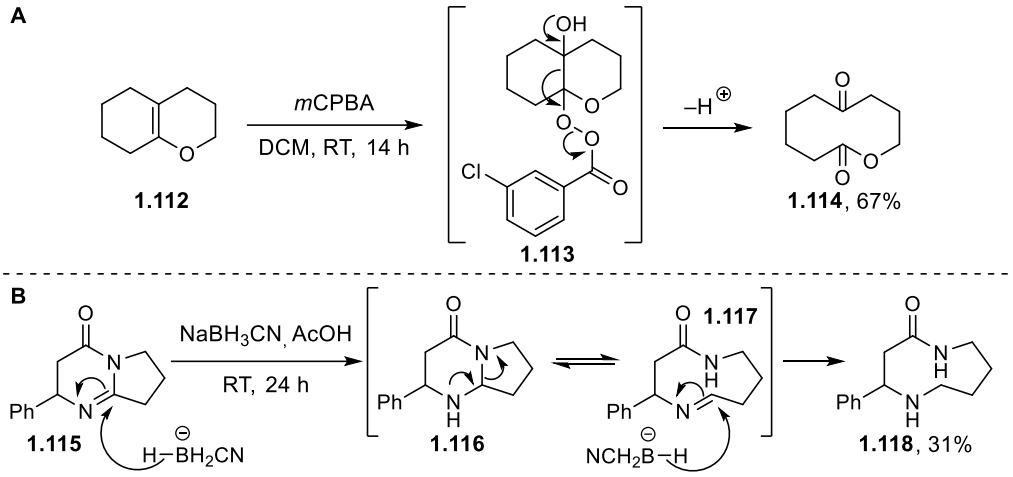
1.108b gave 11-membered product **1.111b** in 69% yield and required a longer reaction time, suggesting there is a lower thermodynamic driving force in this example. Ring expansion of 7-membered lactone **1.108c** appeared to be thermodynamically unfavourable with the 10-membered lactone **1.111c** not being formed during the reaction.



Scheme 17. Translactonisation reaction in the synthesis of macrocyclic lactones.

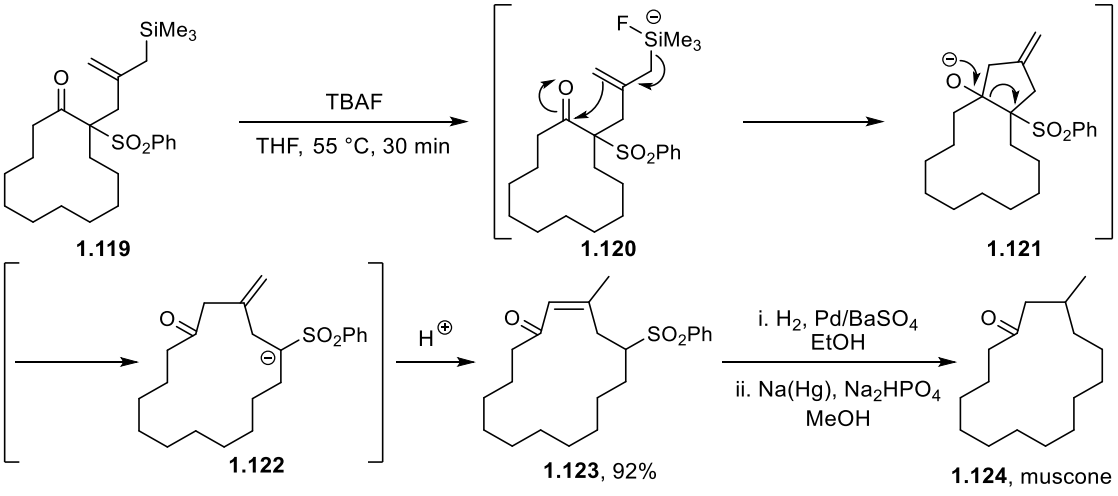
Borowitz and co-workers reported an oxidative cleavage of enol ethers to give medium-sized lactones (Scheme 18A).[37] Enol ether **1.112** was reacted with *m*CPBA resulting in oxidation to hydroxy peroxy ester **1.113**. This can then fragment, cleaving the C–C bond of the fused bicyclic structure leading to 10-membered lactone **1.114** in 67% yield, driven by the formation of two strong C=O bonds at the expanse of one C=C bond.

Reductive cleavages are also possible, as was shown by Wasserman and co-workers in the total synthesis of celacinnine (Scheme 18B).[38] Amidine **1.115** was reacted with sodium cyanoborohydride under acidic conditions, first reduction of the amidine took place to give aminal **1.116**. This exists in equilibrium with medium-sized cyclic imine **1.117**, which can be reduced by a second equivalent of sodium borohydride to give the 9-membered product **1.118**, albeit in low yield. Although demonstrating that reductive cleavage was possible, the low yield prompted the authors to pursue a more efficient route to lactam **1.118**.



Scheme 18. [A] Oxidative fragmentation using *m*CPBA to cleave an alkene. [B] Reductive cleavage of amidines into lactams.

Trost and co-workers reported a fluoride-initiated C–C bond forming ring expansion reaction in the synthesis of muscone (Scheme 19).[39] Reaction of silane **1.119** with tetrabutylammonium fluoride (TBAF) gives pentavalent silyl **1.120**, which can fragment with nucleophilic attack through the carbon atom to give bicyclic intermediate **1.121**. This can then fragment, reforming the ketone and generating the resonance stabilised anion **1.122**. Protonation of the anion gave the product which was found to have undergone isomerisation to the more thermodynamically favourable alkene **1.123**. The synthesis of muscone **1.124** was then completed by hydrogenation of the alkene and reduction of sulfone using sodium amalgam.

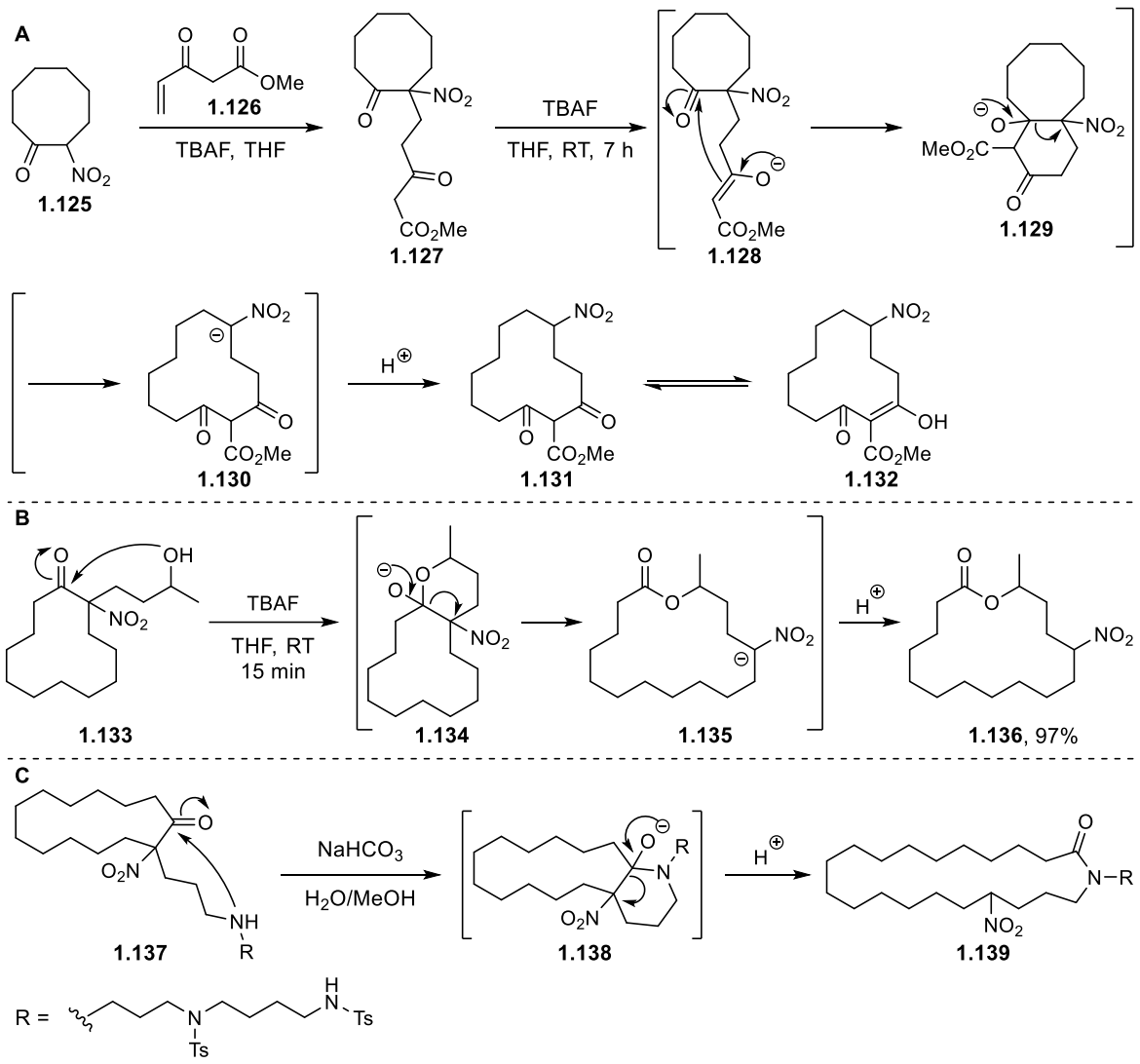


Scheme 19. Fluoride initiated ring expansion reaction in the synthesis of muscone.

The Hesse group reported a large number of ring expansion reactions, particularly in the area of side chain insertions. One example of this is the synthesis of the 12-

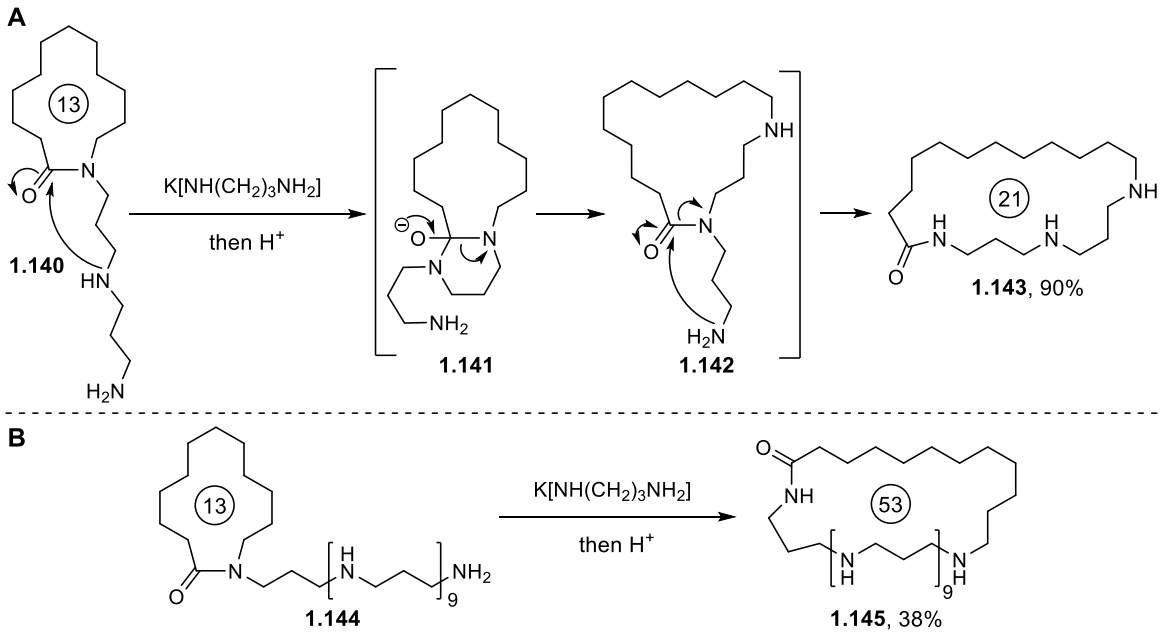
membered ring **1.132**, starting from 8-membered α-nitro ketone **1.125** (Scheme 20A).[40] Michael addition gave β-keto ester **1.127** which upon stirring with a base underwent deprotonation to enolate **1.128**, followed by nucleophilic attack into the carbonyl resulting in the bicyclic intermediate **1.129**. This can then fragment to give resonance stabilised anion **1.130** which upon protonation give the desired 12-membered ring **1.131**/**1.132** as a mixture of the keto and enol tautomers.

The same group also found that both oxygen and nitrogen nucleophiles could be utilised in this reaction. When hydroxy ketone **1.133** was stirred with TBAF, a ring expansion was initiated (**1.133** → **1.134** → **1.135**), which following protonation gave the 4-atom ring expanded lactone **1.136** (Scheme 20B).[41] The nitrogen-based nucleophile **1.137** also underwent ring expansion *via* the same mechanism (**1.137** → **1.138** → **1.139**) to give 21-membered lactam **1.139** (Scheme 20C).[42] A second ring expansion was attempted on this product by removing the tosyl groups, however this resulting in an equilibrium mixture of the 21-membered lactam **1.139** and the 25-membered lactam, with the smaller ring being the major component.



Scheme 20. Ring expansion *via* side chain insertion using carbon, oxygen and nitrogen nucleophiles.

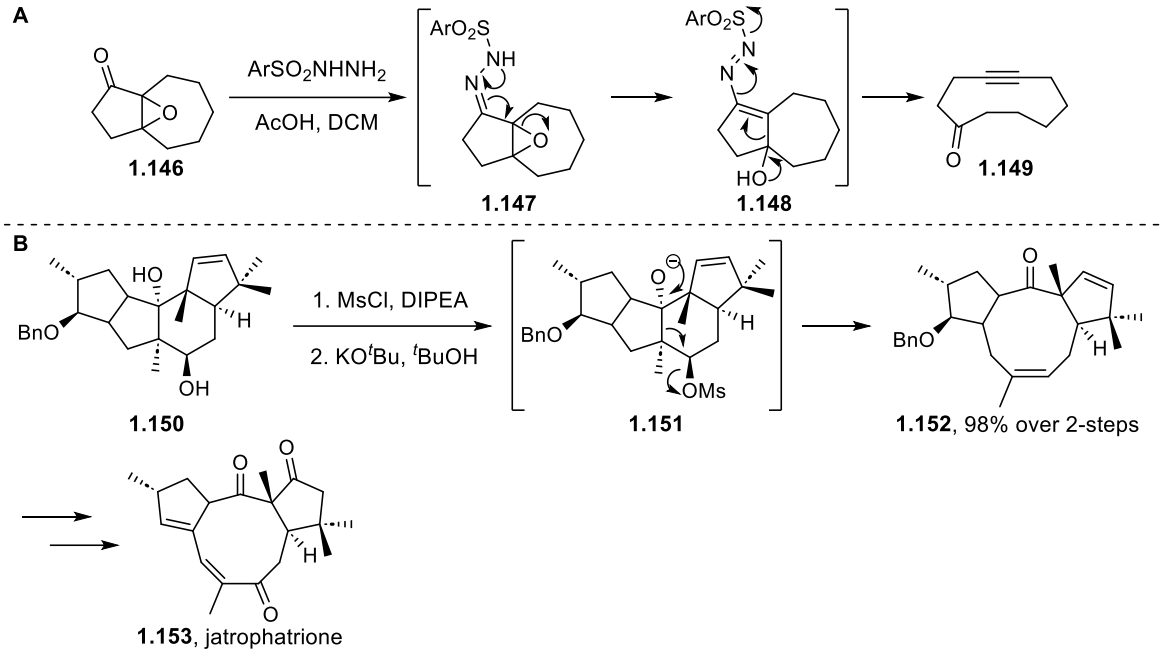
The Hesse group also reported a ring expansion cascade that they termed the "Zip" reaction.[43] In this reaction, a lactam with a polyamine side chain, such as lactam **1.140**, is stirred with a potassium amide base which initiates the transamidation cascade (Scheme 21A). The first nitrogen of the side chain attacks into the carbonyl forming a 6-membered bicyclic intermediate **1.141** which fragments into macrocycle **1.142**, completing the first ring expansion. Next, the second nitrogen of the side chain can attack into the carbonyl again forming a 6-membered bicyclic intermediate that fragments giving the final 21-membered lactam **1.143**. To demonstrate the potential of this reaction, precursor **1.144** was synthesised, containing ten amine groups on the side chain (Scheme 21B).[44] This was then reacted under the standard reaction conditions and underwent successive transamidation to yield the 53-membered lactam **1.145** in an impressive 38% yield.



Scheme 21. "Zip" reaction used to synthesise macrocycles up to 53-membered.

The well-known Eschenmoser fragmentation has also been utilised in ring expansion reactions, for example Danishefsky and co-workers used this reaction to synthesise cyclic alkynes (Scheme 22A).[45] Ketone **1.146** underwent a condensation reaction with a sulfonyl hydrazide to give hydrazone **1.147**. Ring opening of the epoxide gave hydroxide **1.148** which could fragment by cleavage of the fused bicyclic rings and C–N bond giving the alkyne product **1.149**. Release of nitrogen gas during this process provides a strong thermodynamic driving force for the reaction.

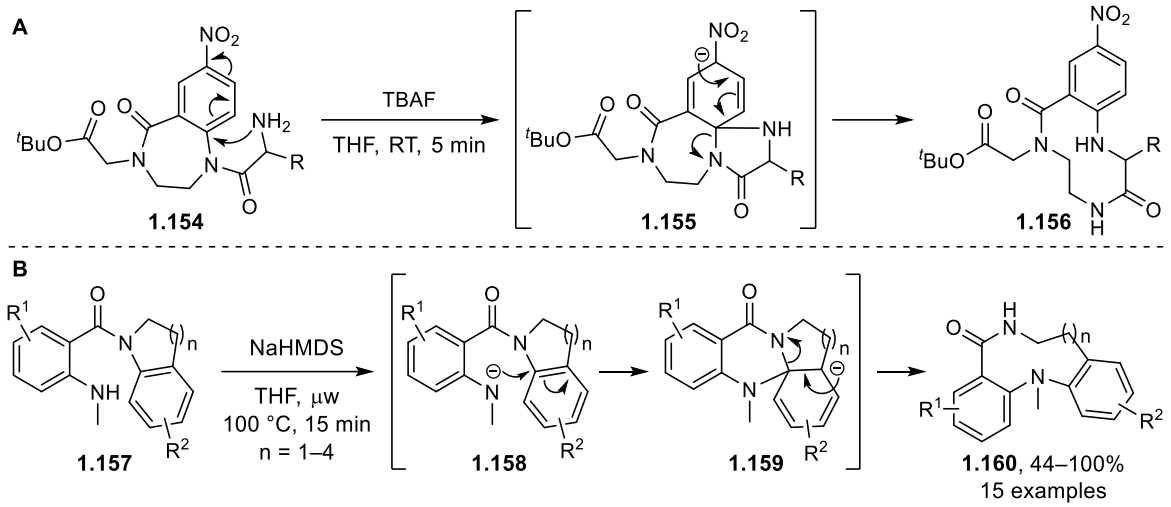
The similar Grob fragmentation has also been used to synthesise cyclic alkenes, as was the case in the total synthesis of jatrophatrione by Paquette and co-workers (Scheme 22B).[46] By selectively mesylating the secondary alcohol of diol **1.150**, as opposed to the tertiary alcohol, the authors could initiate a Grob fragmentation by reaction with potassium *tert*-butoxide. Deprotonation of the alcohol gave alkoxide **1.151** which can undergo an elimination, fragmenting the bicyclic system and forming 9-membered cyclic alkene **1.152**. This provided an efficient route to install the key 9-membered ring of jatrophatrione.



Scheme 22. [A] Eschenmoser fragmentation used to synthesise 10-membered cyclic alkynes. [B] Grob fragmentation for the synthesis of cyclic alkenes and applied to the total synthesis of jatrophatrione.

Still and co-workers reported a Smiles rearrangement for the synthesis of 10-membered lactams (Scheme 23A).[47] Stirring amine **1.154** with TBAF resulted in attack of the amine into the aromatic ring to give intermediate **1.155**. This then fragments, with the amide nitrogen leaving preferentially due to being the more stable anion, giving the product **1.156**. This method allowed the insertion of an amino acid unit into an existing ring, although the S_NAr reaction required strong electron withdrawing groups, with examples being limited to substrates with a *para*-nitro group on the aromatic ring.

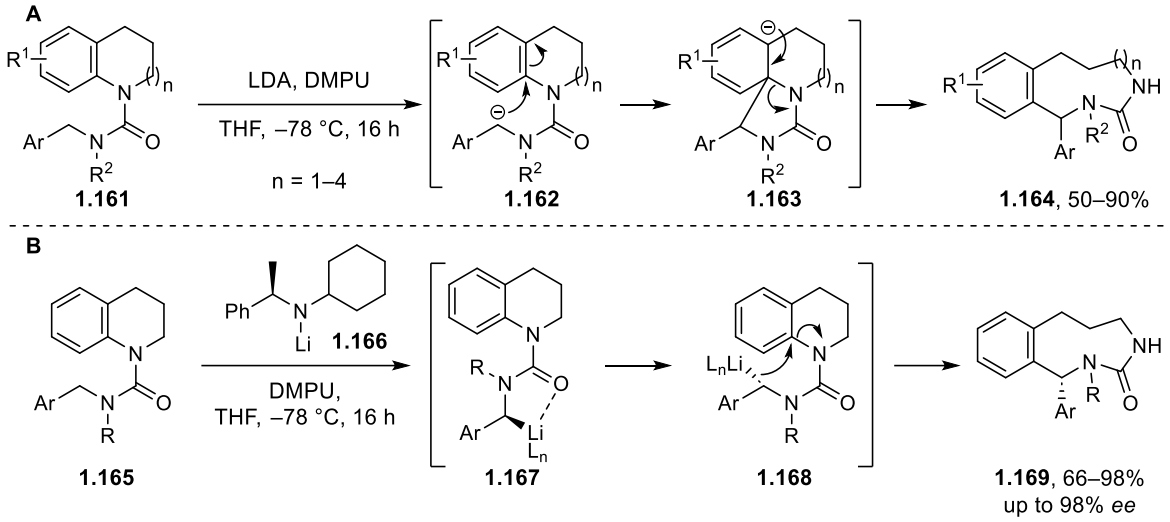
Clayden and co-workers also reported the use of a Smiles rearrangement for ring expansion (Scheme 23B).[48] In this work an aniline **1.157** was reacted with NaHMDS to give anion **1.158**, which attacks into the aromatic ring system and then fragments to give lactam **1.160** following protonation. Notably, there was no requirement for electron withdrawing groups on the aromatic ring (R^2) in these examples. The authors propose that this is due to the tertiary anilide which preorganises the substrates, placing the nucleophilic group close to the electrophilic ring, although elevated temperatures were still required.



Scheme 23. [A] Smiles rearrangement used for the insertion of an amino acid unit. [B] Smiles rearrangement ring expansion that did not require electron with drawing substituents (R^2).

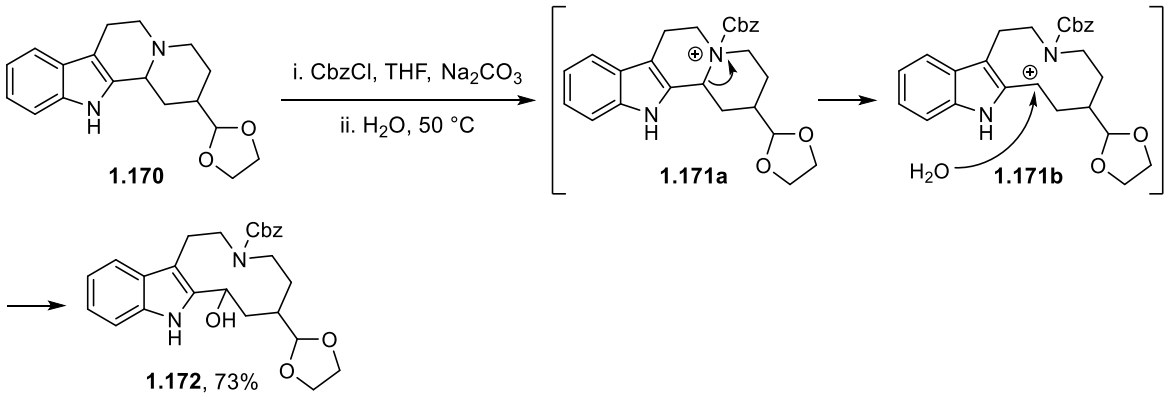
Clayden and co-workers have also reported a Smiles-type rearrangement in which a carbon-based nucleophile is used (Scheme 24A).[49] Urea **1.161** can be deprotonated using LDA to give anion **1.162**. This then reacts in the same way as the previous example, first attacking the aromatic ring, and then fragmenting to give the cyclic urea products **1.164**. Again, electron withdrawing groups were not required on the aromatic ring, and in fact the reaction proceeded efficiently even with electron donating groups (R^1 = OMe).

The same group later expanded on this work by reporting a stereoselective ring expansion (Scheme 24B).[50] The authors propose that the enantioselective formation of benzyl lithium species **1.167** is followed by rapid stereochemically retentive S_NAr to give the desired urea products **1.169**. Products were isolated in good yields and in most cases with good enantiomeric excess (*ee*) of up to 98%.



Scheme 24. [A] Smiles-type rearrangement used to synthesis 8–12-membered cyclic ureas. [B] Stereoselective ring expansion using a chiral lithium base.

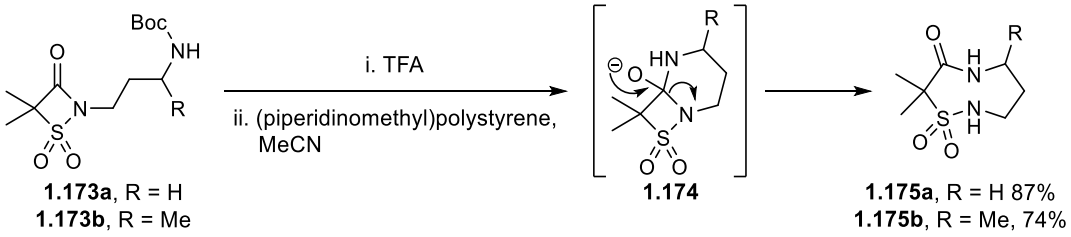
Bonjoch and co-workers reported an interesting ring expansion in the synthesis of the natural product (±)-deethylibophyllidine (Scheme 25).[51] Bicyclic amine **1.170** was first reacted with benzyl chloroformate to give ammonium **1.171a**, which can fragment to give carbocation **1.171b**. Water was added to the reaction to trap the carbocation intermediate **1.171b**, giving the ring expanded product **1.172** in 73% yield. This was the most efficient route to the target natural product, however different alkylating/acylating reagents (*e.g.* methyl iodide) and nucleophiles (*e.g.* sodium cyanoborohydride) were used by this group and others.[51–53]



Scheme 25. Amine acylation followed by bicyclic fragmentation to give 10-membered cyclic amine.

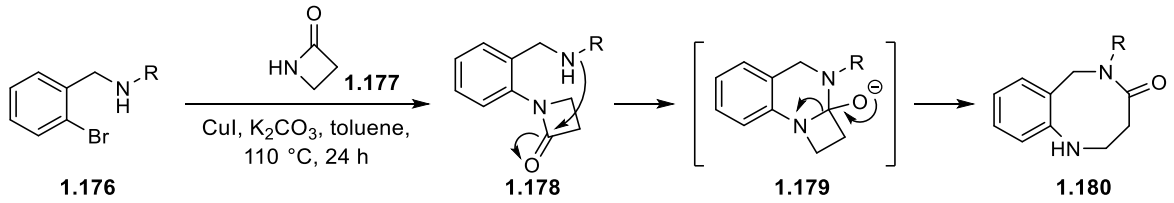
Ring expansion of cyclic sulfonamides is also possible, as was reported by Heimgartner and co-workers (Scheme 26).[54] Protected amine **1.173** was reacted with TFA to give the corresponding ammonium salt, which when basified with a polymer base underwent ring expansion to give the 8-membered sulfonamide **1.175**. An interesting

observation in this reaction is that the amine nucleophile can attack two electrophilic positions, the C=O or S=O bond. When using an unsubstituted amine (R = H), attack at both positions leads to the same product. To identify which of these positions is attacked, α-substituted amine **1.173b** was used, and it was found that **1.175b** was the only observable product, meaning that attack occurs exclusively at the carbonyl position (*via* intermediate **1.174**).



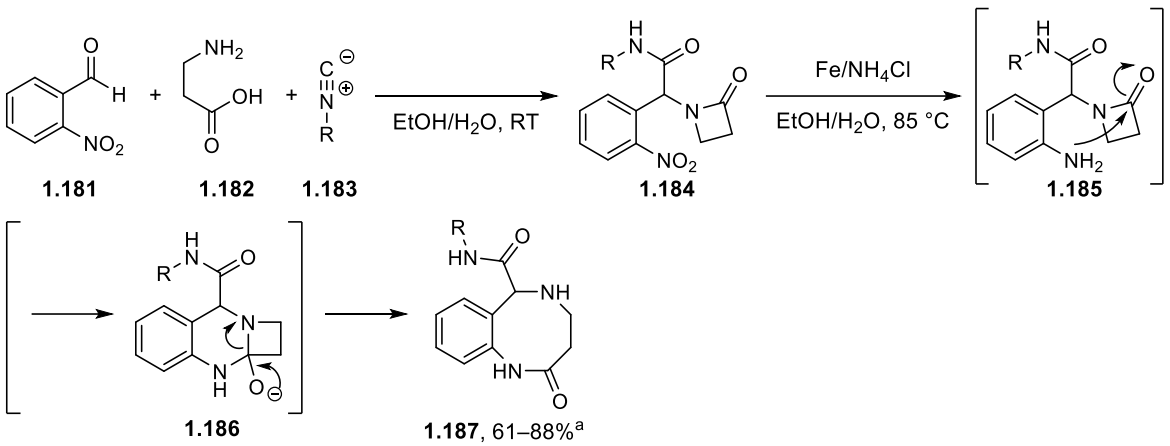
Scheme 26. Ring expansion of sulfonamide containing precursors.

Buchwald and co-workers reported a cascade process, consisting of a copper catalysed coupling followed by ring expansion, for the synthesis of medium-sized lactams (Scheme 27).[55] First, azetidinone **1.177** was coupled to aryl bromide **1.176**, following which the ring expansion took place. Attack of the amine nucleophile into 4-membered lactam **1.178** gave the bicyclic intermediate **1.179**, which fragments relieving the ring strain of the 4-membered ring and giving 8-membered lactam **1.180**. In cases where secondary amines with bulky substituents (R) were used, ring expansion did not take place following coupling, instead lactams **1.178** were isolated and required the use of a Lewis acid catalyst to encourage ring expansion.



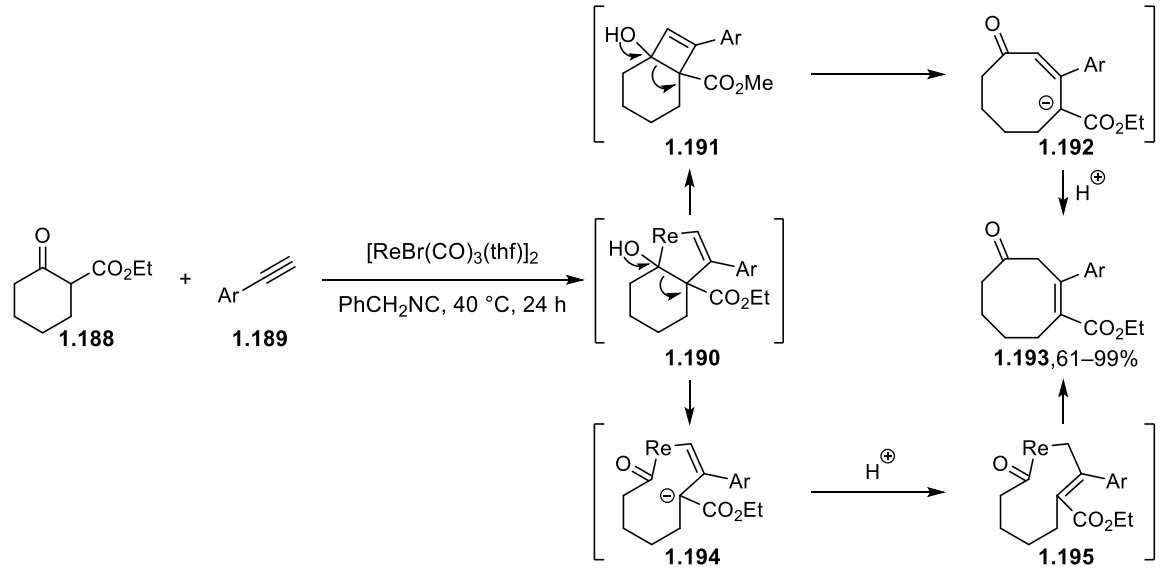
Scheme 27. Copper catalysed coupling followed by ring expansion.

A similar reaction was reported by Chattopadhyay and co-workers who utilised the multicomponent Ugi reaction to generate the prerequisite 4-membered lactam **1.184** (Scheme 28).[56] Following this, the nitro group was reduced using Fe/NH_4Cl to give aniline **1.185** which underwent ring expansion (**1.185** → **1.186** → **1.187**) to give lactams **1.187** in good yields. Using this method the authors were able to generate a high degree of molecular complexity in a one-pot, two-step procedure.



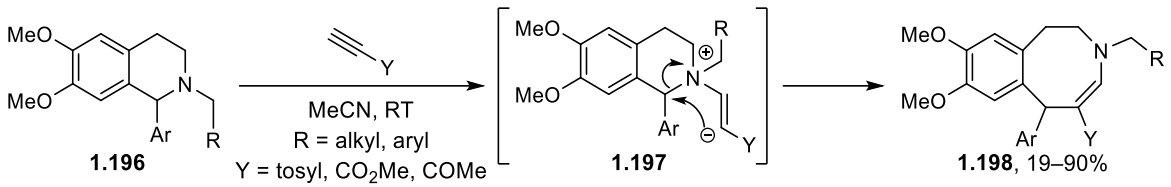
Scheme 28. Ugi Reaction followed by nitro reduction with concomitant ring expansion. [a] Yield over two-steps.

The insertion of alkynes into 6-membered rings has also been reported as a 2-atom ring expansion method. Kuninobu and co-workers developed a high yielding, rhenium catalysed alkyne insertion reaction (Scheme 29).[57] In this reaction a β-keto ester **1.188** and an alkyne **1.189** react with a rhenium catalyst to first form a 5-membered rhenacycle **1.190**. The authors proposed two mechanisms depending on when reductive elimination takes place. In the first, reductive elimination of 5-membered rhenacycle **1.190** gives 4-membered carbocycle **1.191**, which fragments into 8-membered ring **1.192**, and finally protonation gives the product **1.193**. The alternative pathway involves fragmentation of the bicyclic structure first to give 9-membered rhenacycle **1.194**. Protonation followed by reductive elimination then gives the desired product **1.193**.



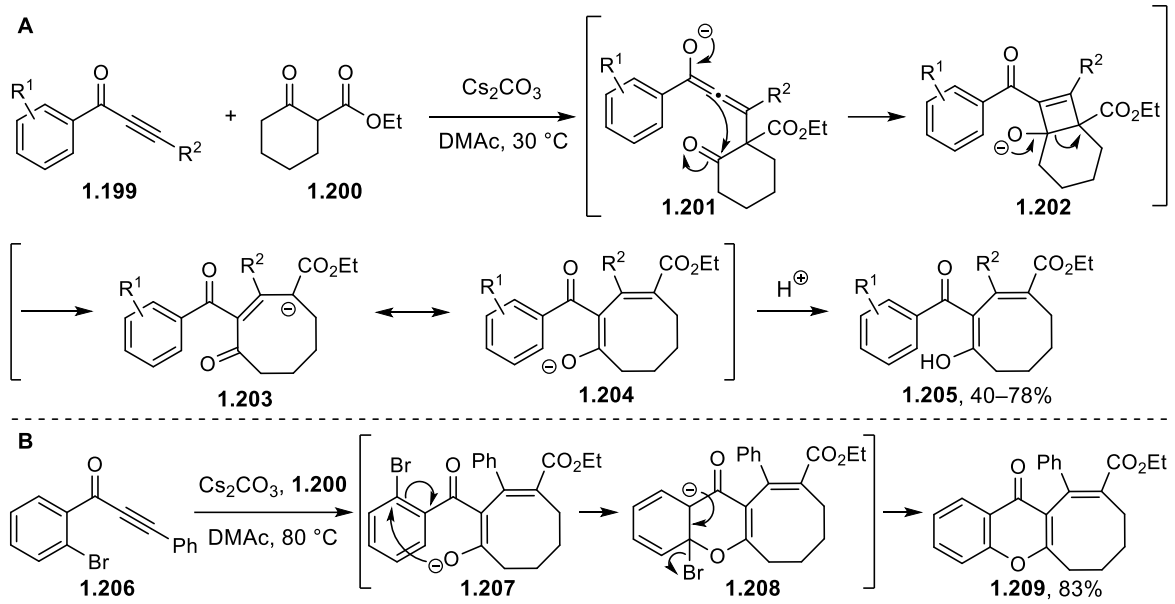
Scheme 29. Alkyne insertion ring expansion utilising a rhenium catalyst.

Voskressensky and co-workers reported the ring expansion of tetrahydroisoquinolines through a conjugate addition and nucleophilic substitution process (Scheme 30).[58] By reacting tetrahydroisoquinolines **1.196** with a conjugated alkyne, the zwitterion **1.197** could be generated. This then undergoes an intramolecular nucleophilic substitution quenching both charged moieties and yielding the 8-membered enamines **1.198**. Alkynes conjugated with ester, ketone and sulfonyl functional groups were all well tolerated, generating the desired products **1.198** typically in good yields.



Scheme 30. Ring expansion of tetrahydroisoquinolines through conjugate addition with alkynes.

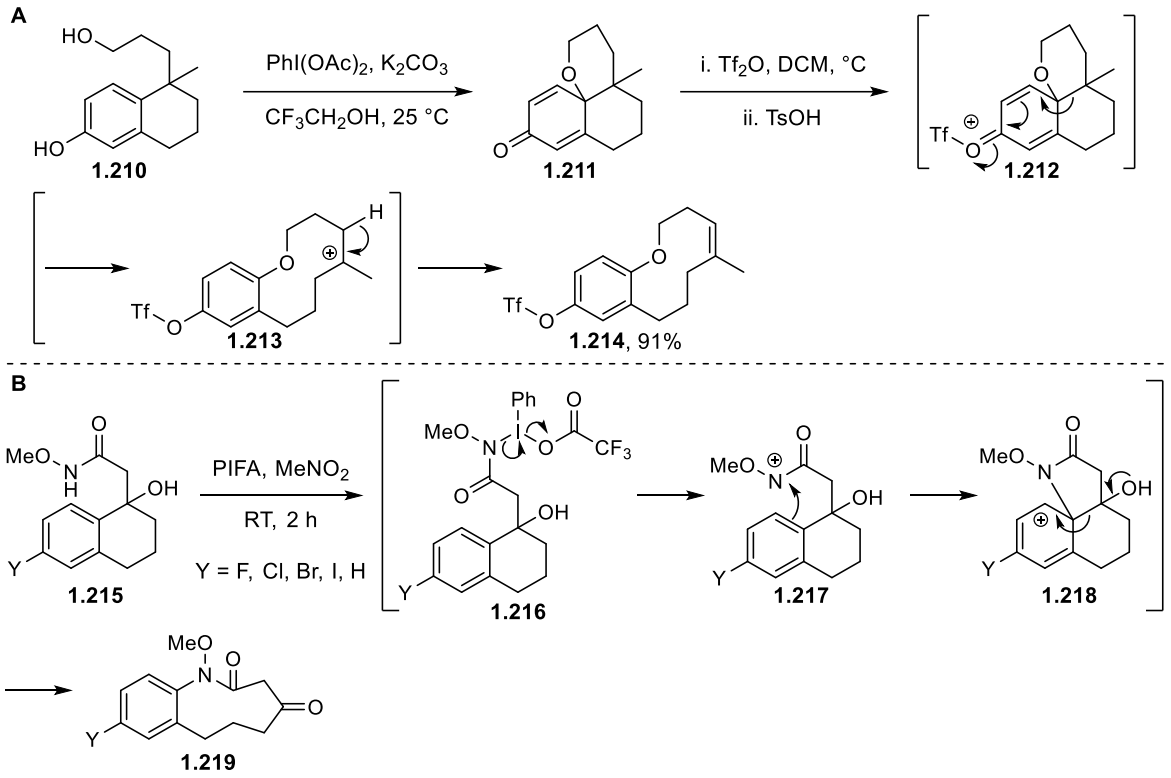
Li and co-workers reported a similar alkyne insertion into a β-keto ester without the need for transition metal catalysts (Scheme 31A).[59] In this work, β-keto ester **1.200** was reacted with a base forming an enolate which underwent conjugate addition with ynone **1.199** to give enolate **1.201**. Intramolecular cyclisation results in bicyclic intermediate **1.202** which fragments into enolate **1.204** and upon protonation gave the 8-membered product **1.205**, typically in good yields. Alternatively, a 4π electrocyclic ring opening of bicycle **1.202** could lead directly to anion **1.204**, although this was not discussed by the authors. Interestingly, when an *ortho*- bromide substituent is incorporated into the ynone precursor **1.206**, an S_NAr reaction takes place after ring expansion (**1.207** → **1.208** → **1.209**) to yield the tricyclic product **1.209** (Scheme 31B).



Scheme 31. [A] Alkyne insertion ring expansion *via* conjugate addition. [B] S_NAr reaction that followed ring expansion when and *ortho*- bromide substituent was present.

Tan and co-workers reported an oxidative dearomatisation-ring-expanding rearomatisation (ODRE) reaction for the synthesis of 8–12-membered rings (Scheme 32A).[60] In this two-step sequence, phenol **1.210** is dearomatized by oxidation to the tricyclic enone **1.211** which is then reacted with triflic anhydride to give oxocarbenium **1.212**. This can then fragment into the 10-membered ring **1.213**, driven by the formation of a tertiary carbocation as well as rearomatisation to the triflate ester. Hydrogen loss then gave a mixture of the three possible regioisomers which converged to a single isomer upon treatment with toluenesulfonic acid.

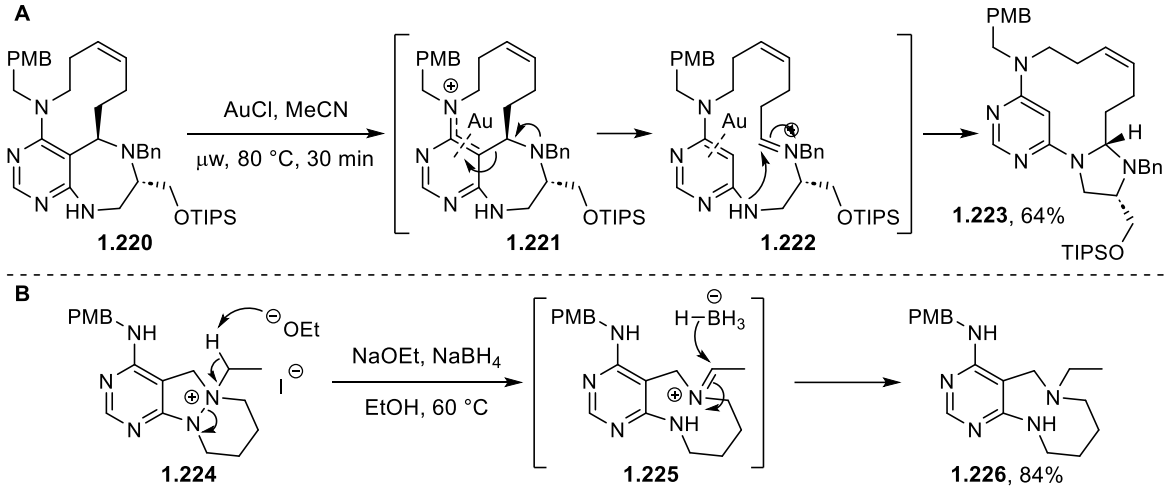
The Tan group further developed this methodology by developing a one-pot ODRE reaction to make lactams (Scheme 32B).[61] In this work, *N*-methoxy amide **1.215** was reacted with hypervalent iodine reagent PIFA to generate nitrenium ion **1.217**, *via* intermediate **1.216**. Electrophilic attack of the aryl group into the nitrenium ion generates intermediate **1.218**. Cleavage of the C–C bond, facilitated by the hydroxyl group, leads to rearomatisation and generation of the desired medium-sized lactam **1.219**. The authors proposed a cationic mechanism for this transformation as the *N*-methoxy group, as well as the nitromethane solvent, are both able to stabilise the intermediate nitrenium cation **1.217**. This new method allowed access to medium-sized lactams without the requirement of having a phenol group, in a single reaction.



Scheme 32. [A] Two-step oxidative dearomatisation-ring-expanding rearomatisation (ODRE) reaction. [B] one-pot ODRE reaction.

Park and co-workers utilised unusual gold reactivity to facilitate a retro-Mannich type C–C bond cleavage, allowing the synthesis of macrocycles (Scheme 33A).[62] Tricyclic pyrimidine **1.220** was reacted with a gold catalyst, which coordinated to the pyrimidine ring to give intermediate **1.221**. This then allows a retro-Mannich type cleavage of the C–C bond to give iminium **1.222**, which then reacts with the anilinic nitrogen to form the 12-membered macrocycle **1.223** in 64% yield.

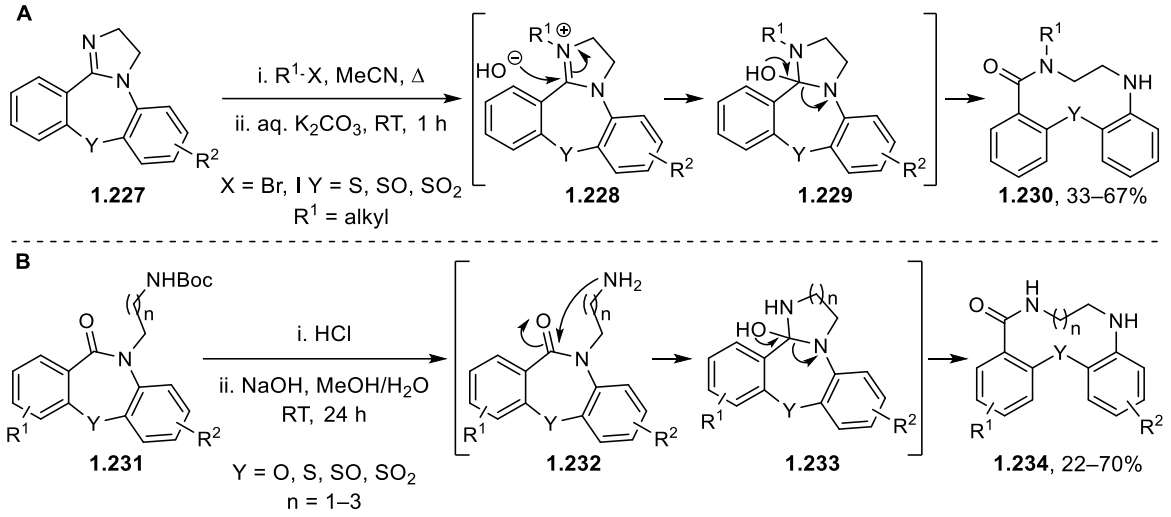
Park and co-workers also reported a different ring expansion reaction, involving the fragmentation of an N–N bond (Scheme 33B).[63] Precursor **1.224** was reacted with a mixture of sodium ethoxide and sodium borohydride, first undergoing deprotonation, followed by fragmentation to the iminium **1.225**. This could then be reduced to give the desired 9-membered amine **1.226** in 84% yield. The group later went on to combine both ring expansion methods sequentially, to generate a diverse library of medium-sized rings and macrocycles.[64]



Scheme 33. [A] Ring expansion utilising a retro-Mannich type C–C bond cleavage facilitated by a gold catalyst. [B] Ring expansion by N–N bond cleavage.

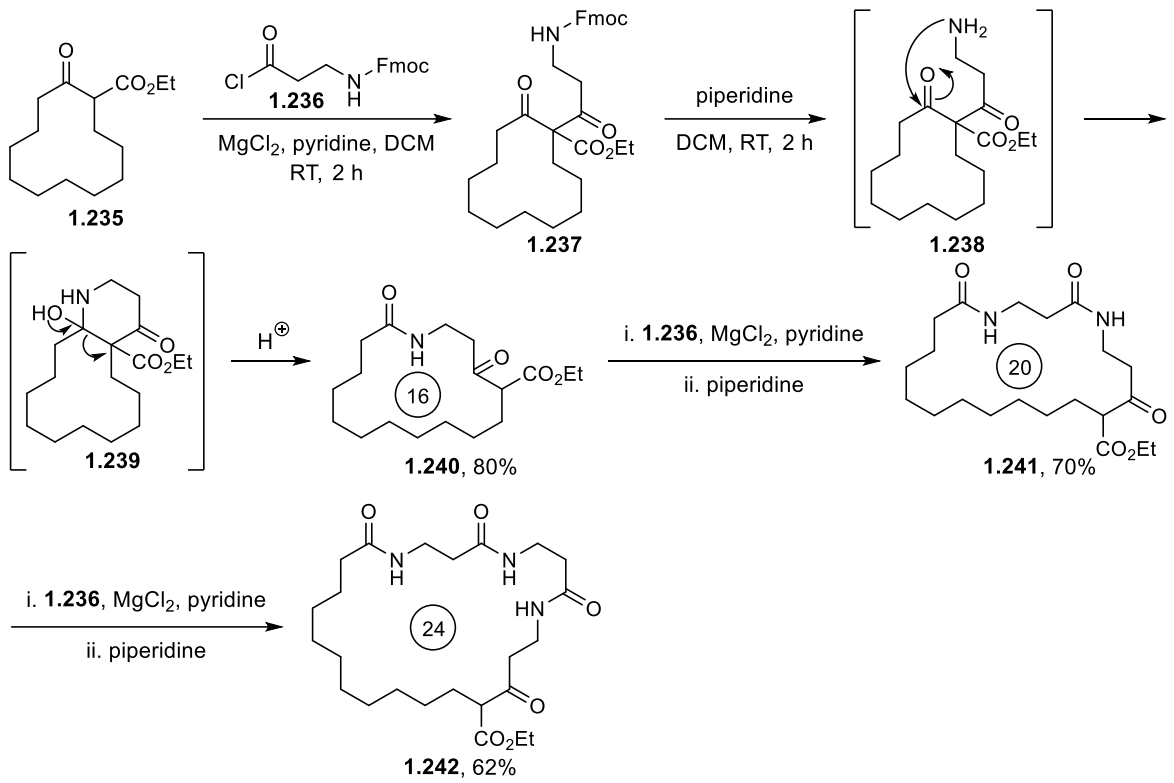
Hydrated imidazoline ring expansion (HIRE) is a methodology developed by Krasavin and co-workers (Scheme 34A).[65] In this work, a fused cyclic amidine **1.227**, is reacted first with an alkyl halide to give imidazolinium **1.228**. This is then reacted with hydroxide to give intermediate **1.229** which fragments into the 10-membered lactam **1.230**. Reaction with an alkyl halide first was found to be essential to facilitate hydrolysis, and without this inclusion, no reaction was observed. Whilst this method gave 10-membered rings in good yields, it was not applicable to any other ring sizes.

The same group later expanded the HIRE methodology to allow the use of tethered amine nucleophiles (Scheme 34B).[66] In this, Boc protected amine **1.231** was first deprotected, then basified to give amine **1.232**. This then attacks into the lactam group forming intermediate **1.233**. Fragmentation then takes place to yield the medium-sized lactams **1.234**. By vary the length of the amine tether the group were able to synthesise 10–12-membered rings, which was not possible in previous work. Yields were typically lower for the formation of 12-membered lactams, likely due to the reaction proceeding through a 7-membered intermediate, however 10/11-mebered lactams were usually formed in high yields.



Scheme 34. [A] Hydrated imidazoline ring expansion (HIRE) for the synthesis of 10-membered lactams. [B] Expansion of the HIRE method allowing the synthesis of 10–12-mebered lactams.

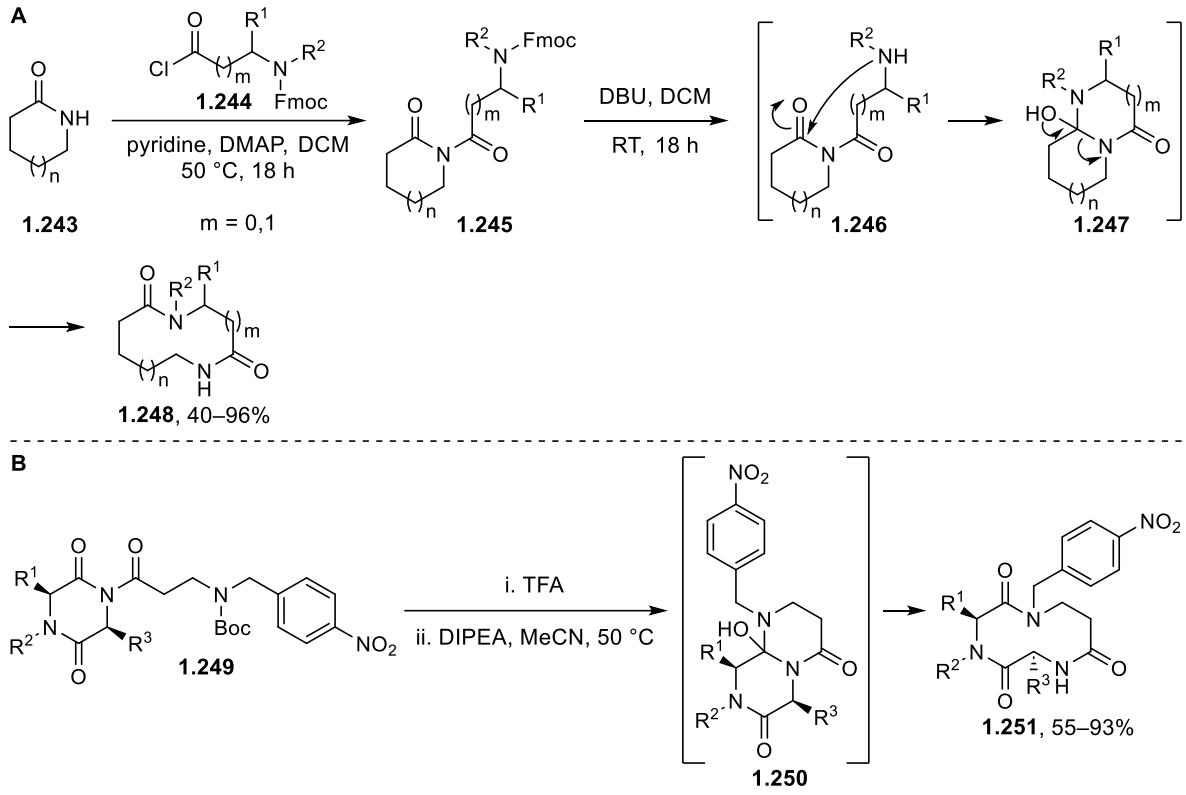
The Unsworth group have reported many examples of ring expansion reactions such as the Successive Ring Expansion (SuRE) method, which they first reported in 2015 (Scheme 35).[67] In this work, a β-keto ester **1.235**, was first acylated giving product **1.237** containing a pendant protected amine. Ring expansion was then initiated by deprotection of amine **1.237**, in this example using piperidine to remove an Fmoc group giving amine **1.238**, although hydrogenolysis of a Cbz protected amine was also demonstrated. Cyclisation then took place giving hemiaminal **1.239** which fragmented, first into the resonance stabilised anion, followed by protonation to give the ring expanded product **1.240**. A key feature of this reaction is that upon generation of the product, the β-keto ester functionality is regenerated, thus allowing subsequent ring expansion reactions to be carried out. This was successfully demonstrated by carrying out two further reactions to give 20-membered macrocycle **1.241**, followed by 24-membered macrocycle **1.242**. Whilst the first publication of this method focused on the synthesis of macrocycles, a later publication demonstrated that this method was equally applicable to the synthesis of medium-sized rings.[68]



Scheme 35. Successive ring expansion (SuRE) that can be used iteratively to synthesise macrocycles.

The Unsworth group further developed the SuRE methodology by using lactam-based precursors **1.243** (Scheme 36A).[69] These could be acylated, similar to the previous β-keto esters, to give imides **1.245**. Deprotection led to amine **1.246** which underwent ring expansion *in situ* (**1.246** → **1.247** → **1.248**) to give ring expanded lactams **1.248**. Like the previous examples, the secondary lactam moiety is regenerated, thus allowing multiple iterations to be carried out, with 3 iterations being the most that was reported to synthesise a 25-membered macrocycle. By utilising lactam precursors, more medicinally relevant cyclic-peptide type structures were able to be synthesised without containing a potentially problematic β-keto ester group.

At the same time, Yudin and co-workers reported a related method using a similar strategy, starting from acylated cyclic dipeptides **1.249** which upon ring expansion gave cyclic tripeptides **1.251** in excellent yields (Scheme 36B).[70] By varying the amino acids used, a range of diversly functionalised tripeptides were able to be synthesised, including unnatural amino acids and different mixtures of D/L-amino acids, without loss of enantiopurity. As with SuRE reactions, the secondary lactam is regenerated during the reaction, although in this case the authors did not report a second ring expansion of any of the products.

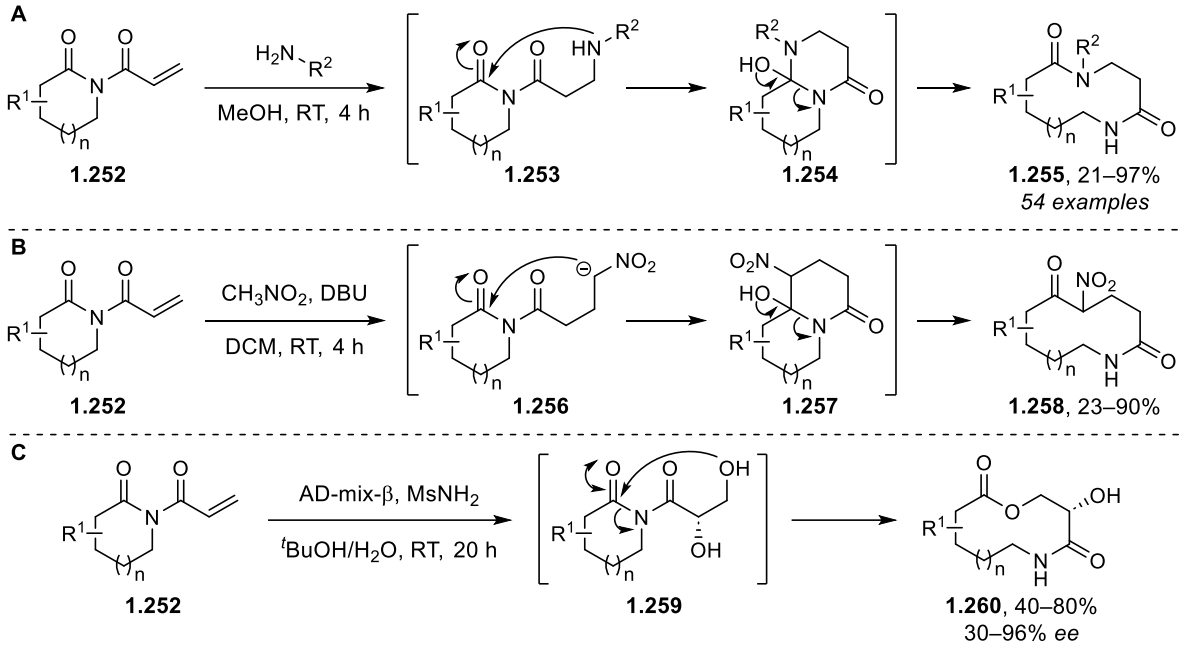


Scheme 36. [A] Successive ring expansion (SuRE) starting from lactams, yielding cyclic peptide-like structures. [B] Synthesis of tripeptides using a SuRE type reaction.

Conjugate Addition/Ring Expansion (CARE) is another ring expansion method developed by the Unsworth group (Scheme 37A).[71] This methodology utilises an acryloyl imide **1.252** which can undergo a conjugate addition reaction with primary amines to give secondary amine **1.253**. This can then cyclise and fragment (**1.253** → **1.254** → **1.255**) to give the ring expanded products **1.255**. One of the main benefits of this method is that protecting groups are not required, thus reducing the overall number of steps in the synthesis and improving its atom economy.

In a later publication this was expanded further by using nitromethane in place of the primary amine (Scheme 37B).[72] This carbon-carbon bond forming ring expansion reaction allowed the synthesis of medium-sized and macrocyclic α-nitro ketones **1.258**. In the same publication,[72] a dihydroxylation ring expansion was also reported, using AD-mix-β (Scheme 37C). Following dihydroxylation of acryloyl imide **1.252** to give diol **1.259**, ring expansion took place to give lactone **1.260**, in which cyclisation of the primary alcohol was favoured. Although not the focus of the work, the products were isolated with modest enantiomeric excess. In all three of these reaction sequences the initial secondary lactam

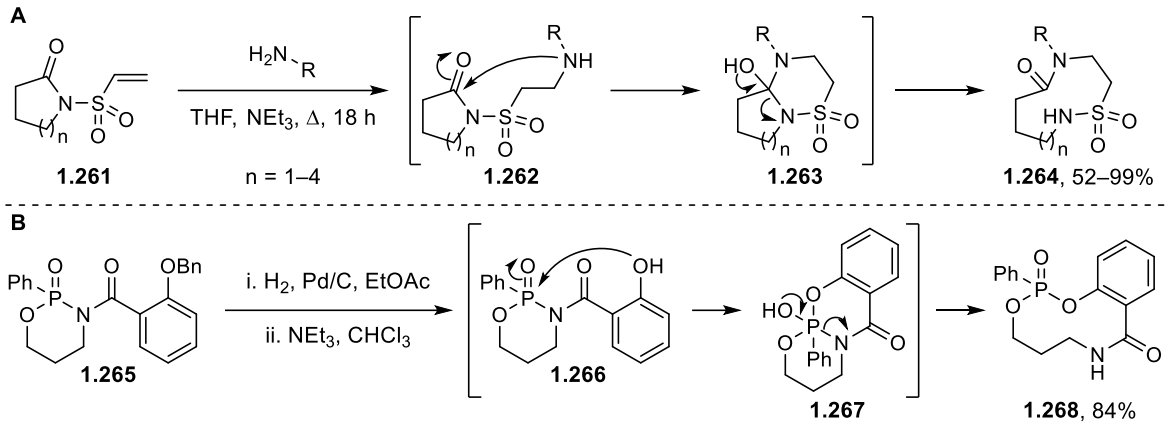
is regenerated, thus allowing these reactions to be performed iteratively which was demonstrated in each case.



Scheme 37. [A] Conjugate addition ring expansion (CARE) reaction using primary amines. [B] CARE reaction using nitromethane. [C] Dihydroxylation ring expansion reaction.

The Unsworth group also showed that the ring expansion reactions they developed can be applied to sulfonamide and phosphonamidate containing precursors. In the former case (Scheme 38A),[73] a conjugate addition reaction utilising a vinyl sulfonamide **1.261** and a primary amine gave secondary amine **1.262**, which cyclised to give intermediate **1.263** and finally fragmented into the desired sulfonamide product **1.264**. This method was successfully applied to the synthesis of 9–12-membered rings in high yields, although yields were typically lower for 9- and 10-membered rings, likely due to the relative stability of the 5- or 6-membered precursors for these ring sizes.

In the ring expansion reaction of phosphonamidates,[74] precursor **1.265** was used which contains a benzyl ether (Scheme 38B). This was removed by hydrogenation to give the alcohol **1.266**, which upon stirring under basic conditions led to the formation of the 10-membered phosphonate **1.268**. This method could also be applied to alkyl alcohol and aniline based nucleophiles, although stirring with a stronger base such as sodium hydride was required following hydrogenation of the benzyl protecting group. P=O containing molecules are present in many drugs, and this is the first time a ring expansion has been used on P=O containing substrates, allowing access to a unique class of molecules.



Scheme 38. [A] Ring expansion reaction to make medium-sized cyclic sulfonamides. [B] Ring expansion reaction of phosphonamidates.

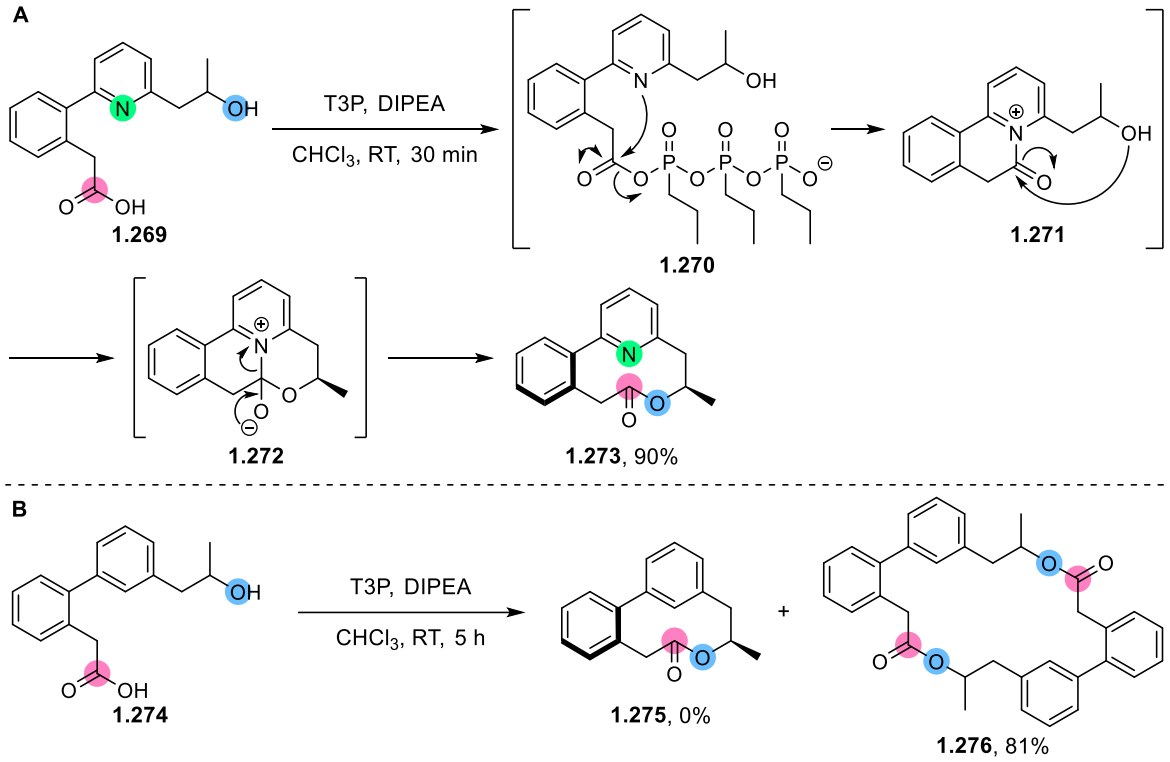
1.5 Cyclisation/Ring Expansion Cascade Reactions

Whilst the previous examples of ring expansion presented all start from cyclic precursors, as might be expected from '*ring*' expansion reactions, this does not necessarily have to be the case. The Unsworth group reported a cyclisation/ring expansion (CRE) cascade reaction that starts from a linear precursor (Scheme 39A).[75] In this work a linear precursor such as carboxylic acid **1.269** is first activated using T3P, this then undergoes an initial cyclisation to give 6-membered intermediate **1.271**. A second cyclisation can then take place giving bicyclic intermediate **1.272**, which fragments with the pyridinium moiety acting as a good leaving group to give the medium-sized ring **1.273**. Using this methodology, 40 examples of lactones and lactams were reported in the Unsworth group's first publication on this method.

The key design feature of this reaction is that all cyclisations take place through "normal"-sized cyclic transition states (5–7-membered). These are likely more kinetically favourable than the macrocyclic analogues and so reactions proceed much for effectively, thus reactions can be carried out at normal dilutions (ca. 0.1 M). In practise this means that substrates for this CRE cascade reaction must contain three components: an electrophile (highlighted pink), an internal nucleophile (highlighted green) and a terminal nucleophile (highlighted blue).

In order to provide evidence for the proposed mechanism, a control reaction was performed (Scheme 39B). In this reaction the precursor **1.274**, was synthesised which lacks the internal nucleophilic pyridyl moiety, thus cyclisation can only take place through direct end-to-end cyclisation. When this substrate was reacted under the CRE cascade reaction

conditions, no evidence of the desired 10-membered ring **1.275** was observed. Instead, only the head-to-tail dimer **1.276** was isolated, strongly suggesting that the internal nucleophile is key to facilitating this cyclisation reaction.



Scheme 39. [A] Cyclisation/ring expansion (CRE) cascade reaction. [B] Control reaction highlighting the importance of the internal nucleophile in the CRE cascade reaction.

One interesting observation made in this publication is that when a biaryl precursor is used (*e.g.* **1.269**), the product is obtained as a single atropisomer. Atropisomers are the result of restricted rotation about a single bond due to steric factors, and typically arise in biaryl molecules contain bulky *ortho*- substituents. In the cases reported by the Unsworth group, the *ortho*- substituents are small, hence the starting materials do not exhibit atropisomers. However, the cyclic nature of the products means that rotation about the biaryl bond is significantly restricted and so atropisomers are observed.

Biaryl atropisomers find a wide variety of uses (Figure 3); BINAP is one example of a chiral ligand used in asymmetric transition metal catalysed reactions such as hydrogenations[76] and Heck reactions.[77,78] Many other related chiral biaryl compounds have also been developed and are often used in palladium, rhodium and ruthenium catalysed reactions.[79–81] Biaryl atropisomers are also used in supramolecular chemistry, for example, biaryl **1.277** is used as a chiral shift reagent allowing the determination of enantiomeric excess of a variety of chiral compounds containing functional groups such as carboxylic

acids, oxazolidinones, lactones, alcohols and sulfoxides by ^{1}H NMR spectroscopy.[1] Biaryl compounds are also pharmaceutically relevant[82–84] with a number of drugs displaying atropisomerism along with a variety of natural products that show this type of stereochemistry.[85]

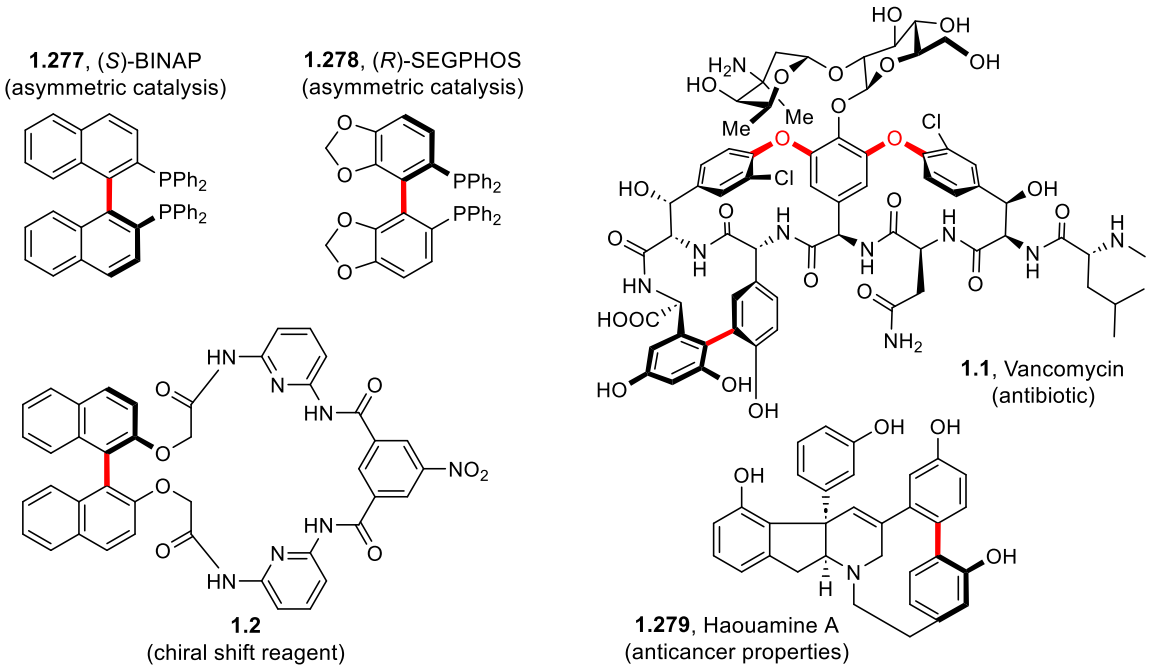
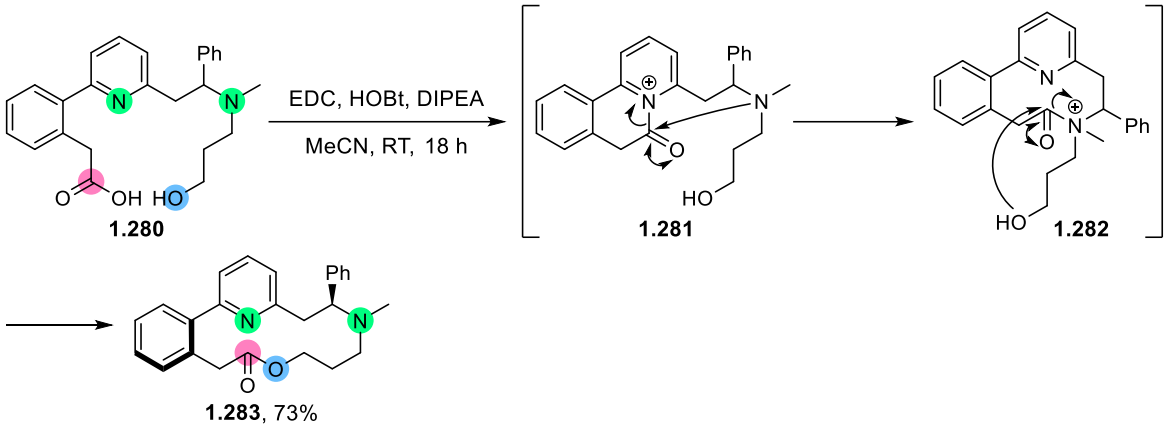


Figure 3. Uses of biaryl compounds with the chiral axis highlighted in red.

This methodology was further expanded through the use of multiple internal nucleophiles, allowing the synthesis of macrocyclic ring systems (Scheme 40).[86] When multiple internal nucleophiles are present, it was proposed that each internal nucleophile cyclises sequentially in a cascade process until the terminal nucleophile cyclises to give the product. This is exemplified in the CRE cascade reaction of hydroxy acid **1.278** which, upon activation of the carboxylic acid with EDC/HOBt, undergoes a first cyclisations to form 6-membered intermediate **1.279**. This is followed by a second cyclisation and fragmentation, through a 6-membered intermediate, to give 10-mebered intermediate **1.280**. This can then undergo a third cyclisation and fragmentation, again through a 6-membered intermediate, to give the final 14-membered lactone **1.281**.



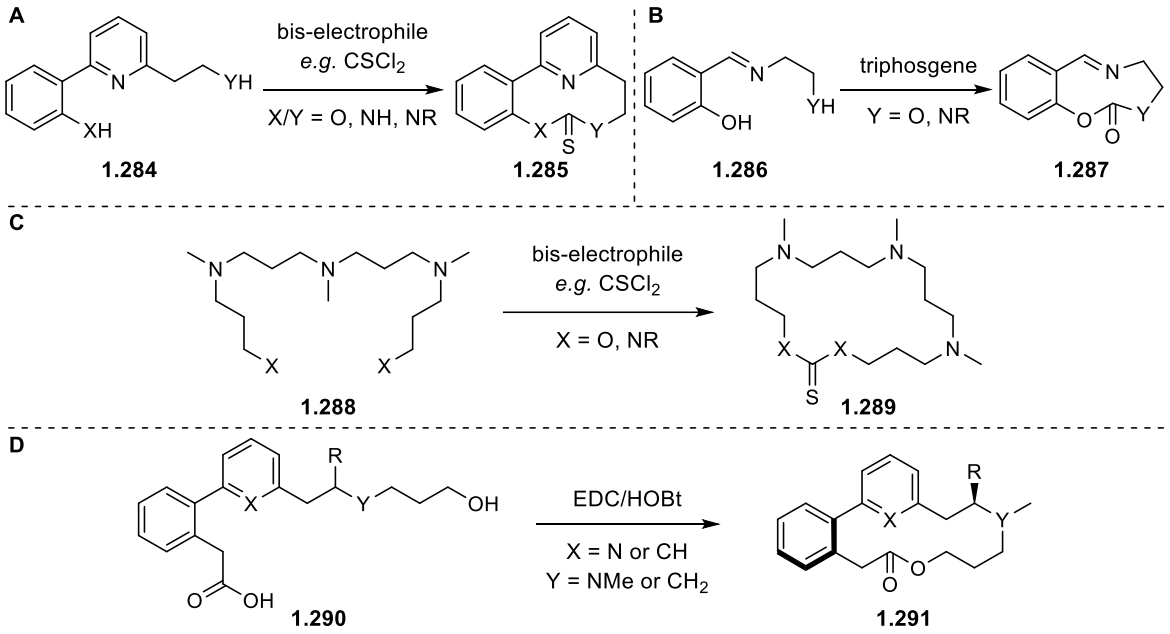
Scheme 40. CRE cascade reaction utilising two internal nucleophiles to synthesise macrocyclic compounds.

1.6 Project Aims

The overall aim of this project was to expand the scope of the CRE cascade reaction, building upon the previous work carried out in the Unsworth group. The Unsworth group have developed a modified CRE cascade reaction that uses bis-electrophilic reagents (*e.g.* thiophosgene) as the electrophilic component. In this thesis, the scope of such CRE cascade reactions using bis-electrophilic reagents has been explored using biaryl containing precursors.

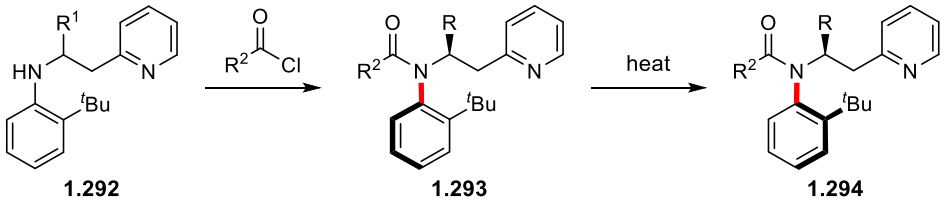
This project also aimed to explore the possibility of using imines as internal nucleophiles, which prior to this PhD project had not been used in the CRE cascade reaction. These substrates present new challenges, such as cyclisation at the iminium position, and so the feasibility of these substrates will be determined. The scope of these substrates was explored using both bis-electrophilic reagents and the classical activated carboxylic acid electrophile.

The use of multiple internal nucleophiles has been demonstrated to be possible previously by the Unsworth group. This project aimed to expand this scope further by utilising bis-electrophilic reagents with substrates containing two, three or potentially five internal nucleophiles. A small number of examples containing multiple internal nucleophiles with an activated carboxylic acid electrophile were also attempted. Control reactions for substrates containing multiple internal nucleophiles had yet to be performed and so control reactions for the above example (**1.280** → **1.283**) were also completed to show the importance of both internal nucleophiles in the cyclisation process. These studies on CRE cascade reactions all feature in Chapter 2 of the thesis.



Scheme 41. Summary of the key project aims.

During the course of this project, it was envisaged that a similar acyl transfer could be applied to the diastereoselective synthesis of atropisomeric anilides, with this work described in Chapter 3 of the thesis. The idea was that this would allow the synthesis of anilides as single diastereoisomers, and the optimisation, scope and limitations of this reaction have all been explored. In order to provide evidence for the acyl transfer mechanism, control reactions were envisaged that should highlight the importance of the pyridyl moiety. DFT calculations were also performed to shed light on the transition states for the acyl transfer reaction and help justify the observed selectivity of the reaction. It was proposed that these atropisomers could undergo thermal epimerisation to the opposite diastereoisomer and this was proven, and the kinetics of this process were also investigated.

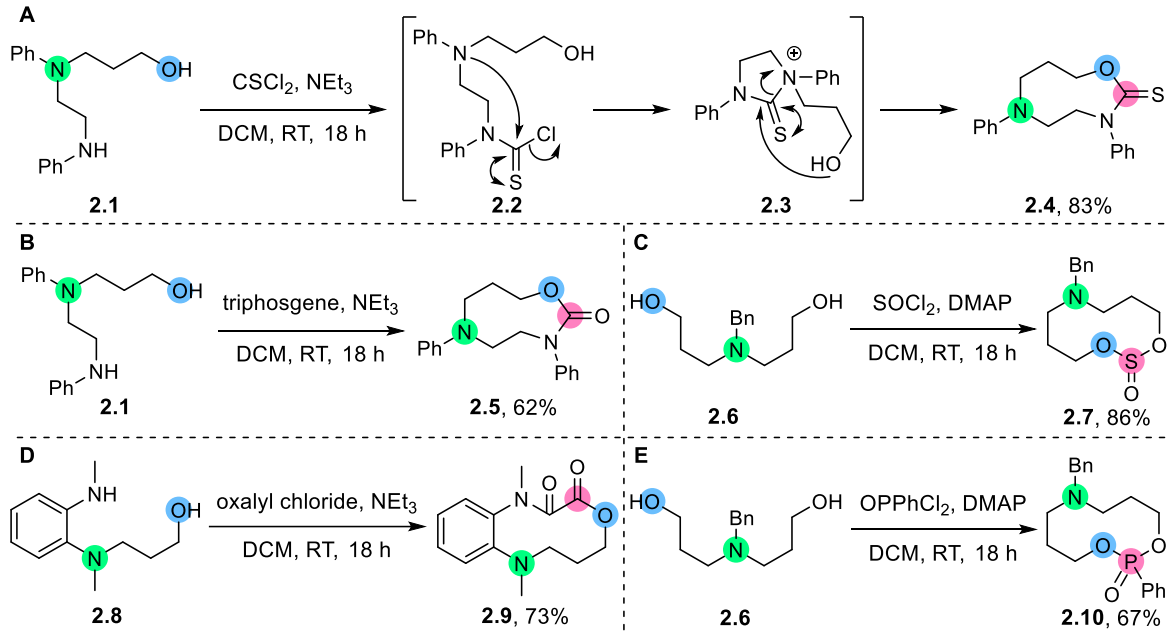


Scheme 42. Proposed diastereoselective acyl transfer reaction to be explored.

2 Cyclisation/Ring Expansion Cascade Reactions

2.1 Cyclisation/Ring Expansion Cascade Reactions Using Bis-Electrophile Reagents

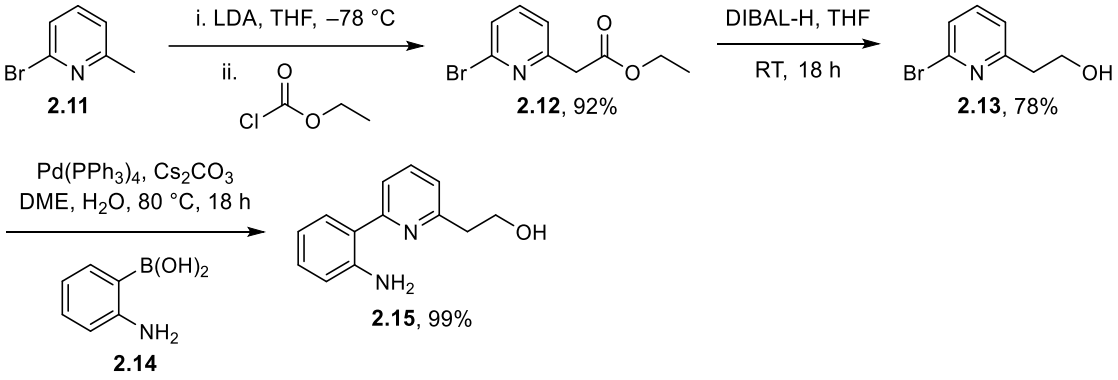
Whilst the previous CRE cascade reactions discussed in Chapter 1.5 were based on activated carboxylic acids as the electrophile, the Unsworth group also developed CRE cascade methodologies using bis-electrophilic reagents in place of activated carboxylic acids (Scheme 43). The substrates for these reactions contain an internal nucleophile as well as two terminal nucleophiles, one such example being amino alcohol **2.1**. When reacted with thiophosgene the more reactive secondary amine nucleophile of **2.1** reacts first giving thiocarbamoyl chloride **2.2**. The internal nucleophile can then cyclise giving cationic 5-membered intermediate **2.3**, which undergoes a second cyclisation, with the terminal alcohol, and fragmentation to give 9-membered thiocarbamate **2.4** (Scheme 43A). Various other functional groups can be installed *via* similar approaches, by utilising different reagents such as triphosgene (Scheme 43B), thionyl chloride (Scheme 43C), oxalyl chloride (Scheme 43D), and phenylphosphonic dichloride (Scheme 43E).



Scheme 43. CRE cascade reactions using bis-electrophilic reagents.

2.2 Synthesis of Biaryl Precursors for the Cyclisation/Ring Expansion Cascade Reaction Using Bis-Electrophilic Reagents

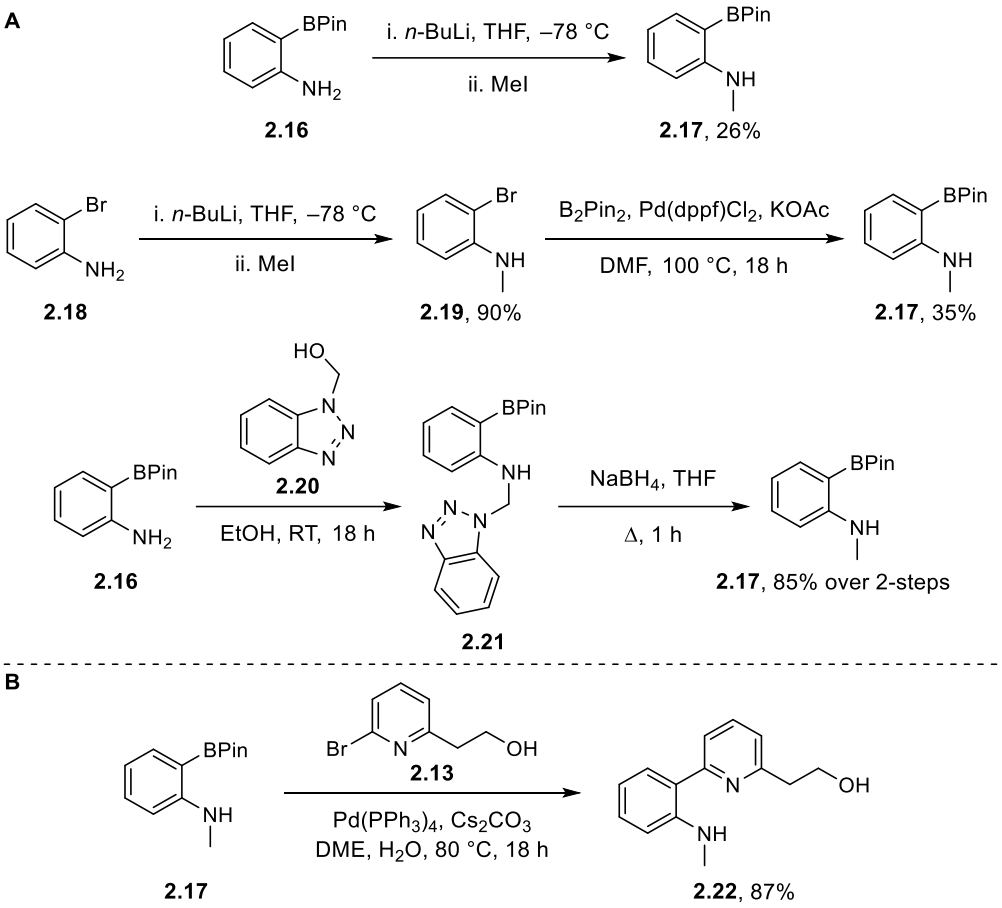
Whilst the Unsworth group had successfully developed CRE cascade reactions using bis-electrophilic reagents prior to this PhD project, the scope of these reactions was limited. Therefore, we set out to expand this scope by first exploring the possibility of using biaryl containing substrates. The first biaryl precursor (**2.15**) to be synthesised contained a primary aniline and alcohol terminal nucleophile with a pyridine internal nucleophile. The synthesis (Scheme 44) started by deprotonation of methylpyridine **2.11** with LDA and then trapping the intermediate organolithium with ethyl chloroformate to give ester **2.12** in 92% yield. This was then reduced using DIBAL-H to give the alcohol **2.13** in 78% yield. Bromopyridine **2.13** was then coupled with 2-aminophenylboronic acid **2.14** in a Suzuki-Miyaura cross-coupling reaction which gave the desired product **2.15** in 99% yield.



Scheme 44. Synthesis of a biaryl containing CRE cascade reaction precursor.

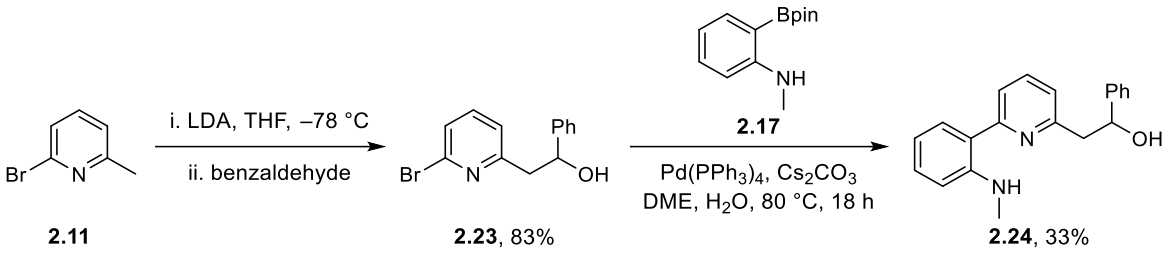
A secondary aniline precursor was also synthesised. Several methods were investigated for the synthesis of *N*-methyl aniline **2.17** (Scheme 45A), the first involved deprotonating aniline **2.16** with *n*-BuLi, followed by addition of methyliodide which gave the methylated product **2.17** in only 26% yield.[87] The low yield of this reaction could be due to the *n*-BuLi reacting with the boron moiety, causing unwanted side reactions and/or hindering deprotonation of the aniline. The next method involved methylating 2-bromoaniline **2.18** using *n*-BuLi and methyliodide, which proved to be much more successful than the boronic ester analogue, affording the product **2.19** in 90% yield. This was followed by a Miyaura borylation to generate the boronic ester **2.17**, in a relatively low yield of 35%.

The final method tested was much more successful and consisted of the condensation reaction of aniline **2.16** with 1-hydroxymethylbenzotriazole **2.20** followed by the reduction of aminomethylbenzotriazole **2.21** with sodium borohydride to yield the desired *N*-methylated boronic ester **2.17** in 85% yield over two-steps.[88] The synthesis of the CRE cascade reaction precursor was completed by performing a Suzuki-Miyara cross-coupling reaction of bromopyridine **2.13** and boronic ester **2.17** to give biaryl **2.22** in 87% yield (Scheme 45B).



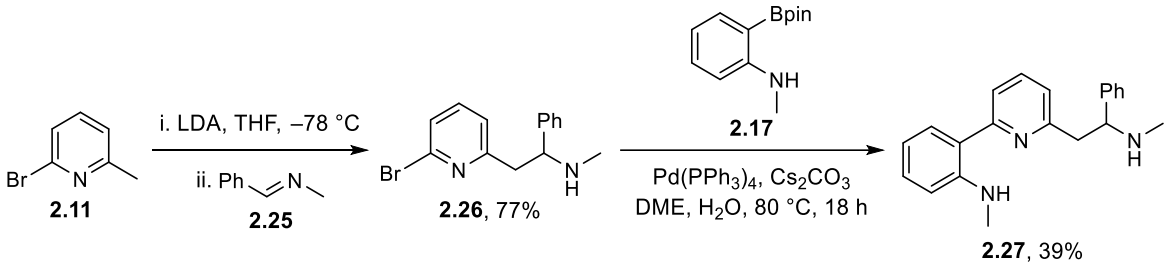
Scheme 45. [A] Different routes to the *N*-methylated boronic ester **2.17**. [B] Suzuki-Miyaura reaction to complete the synthesis of the CRE cascade reaction precursor.

A precursor containing a secondary alcohol was also synthesised (Scheme 46) by first deprotonating methylpyridine **2.11** with LDA followed by subsequent trapping of the lithiated intermediate with benzaldehyde to give alcohol **2.23** in 83% yield. Suzuki–Miyaura cross-coupling was then carried out with bromide **2.23** and boronic ester **2.17** to give the biaryl product **2.24** in 33% yield.



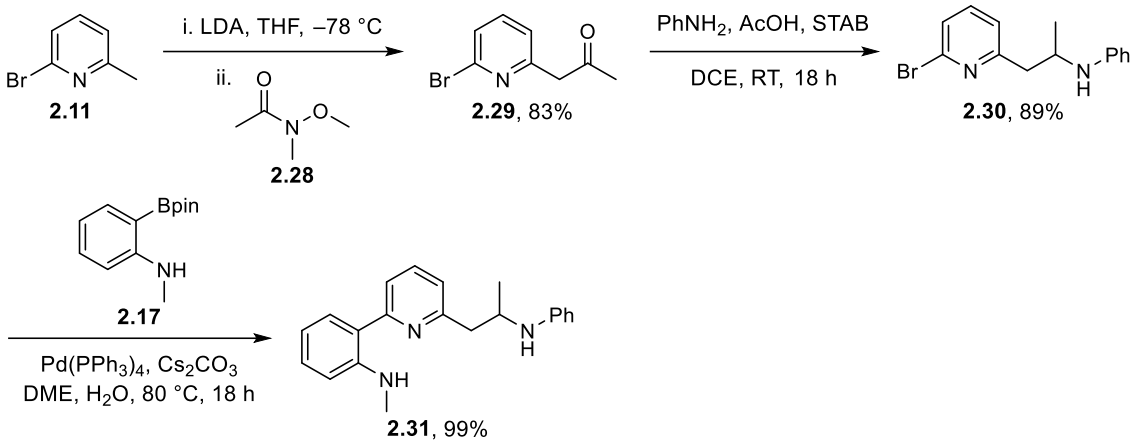
Scheme 46. Synthesis of a secondary alcohol containing precursor.

The next precursor was synthesised *via* a similar procedure (Scheme 47) where methylpyridine **2.11** is deprotonated with LDA then reacted with *N*-benzylidenemethylamine **2.25** to give secondary amine **2.26** in 77% yield. This was then used in a Suzuki-Miyaura cross-coupling reaction with the previously synthesised boronic ester **2.17** to give the desired biaryl **2.27** in 39% yield. The low yield of this reaction is mainly due to the purification steps as after the first purification by column chromatography there was significant amounts of triphenylphosphine oxide and some minor aromatic impurities. The triphenylphosphine oxide is likely the result of oxygen present in the reaction, possibly due to improper degassing of the solvent, and although there appeared to be good separation by TLC, co-elution was observed during column chromatography. Ultimately the impurities were separated by using 5% triethylamine in diethyl ether as the eluent, although in total, column chromatography was carried out five times on the same material and this likely resulted in the loss of significant amounts of product.



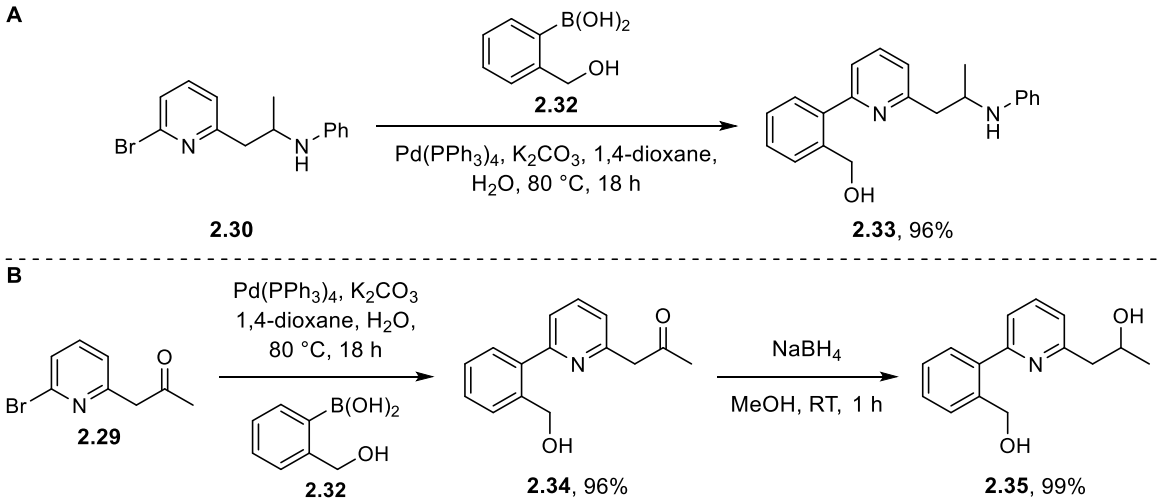
Scheme 47. Synthesis of a CRE cascade reaction precursor bearing two amine nucleophiles.

A precursor bearing two aniline terminal nucleophiles was also synthesised (Scheme 48). First, methylpyridine **2.11** was deprotonated with LDA and the intermediate was trapped using Weinreb amide **2.28** to give the monoacylated product **2.29** in 83% yield. Reductive amination with aniline and subsequent Suzuki-Miyaura cross-coupling with boronic ester **2.17** gave the desired precursor **2.31**, containing two aniline nucleophiles, in high yield over both steps.



Scheme 48. Synthesis of a CRE cascade reaction precursor containing two aniline nucleophiles.

The final two biaryl precursors were synthesised by technician Lee Duff according to the routes shown in Scheme 49. For the first precursor, Suzuki-Miyaura cross-coupling with bromopyridine **2.30** and boronic acid **2.32** gave the desired precursor **2.33**, containing an aniline and an alcohol nucleophile, in 96% yield. The second precursor was synthesised by cross-coupling bromopyridine **2.29** with boronic acid **2.32**, followed by reduction of the ketone to give diol **2.35** in near quantitative yield over both steps.

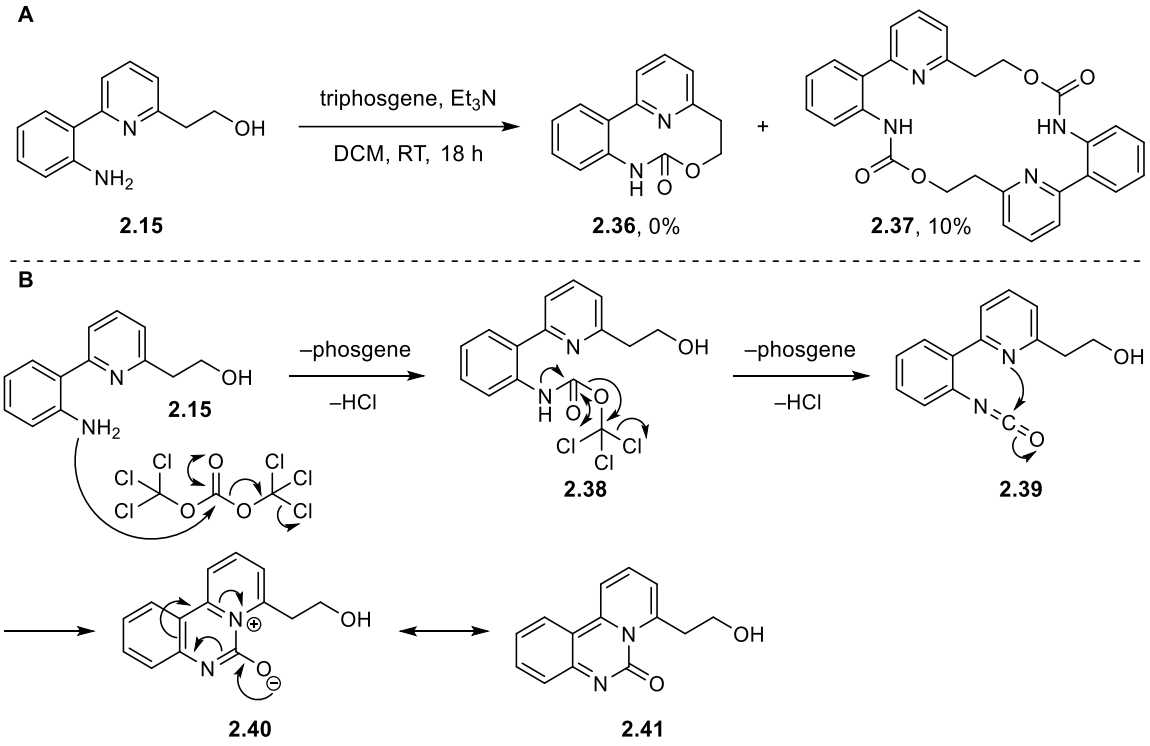


Scheme 49. Synthesis of the final two biaryl precursors, carried out by technician Lee Duff.

2.3 Cyclisation/Ring Expansion Cascade Reactions of Biaryl Containing Precursors

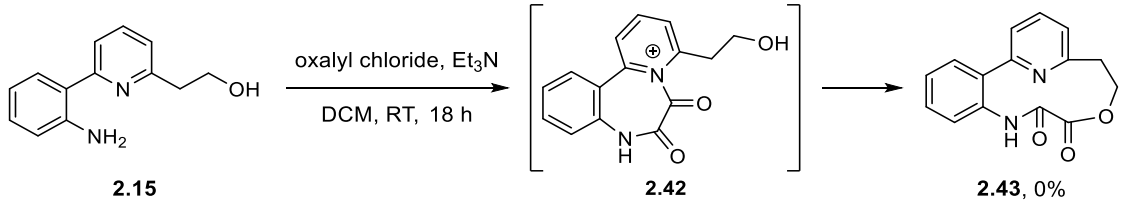
The first CRE cascade reaction was attempted with precursor **2.15** using triphosgene (Scheme 50A), however, the only product that could be isolated was dimer **2.37** in 10% yield. One possible reason for this reaction not working is that triphosgene can lead to the formation of isocyanate intermediate **2.39** (Scheme 50B). This may undergo unwanted side

reactions that do not lead to product formation. One such reaction involves cyclisation to form intermediate **2.40**, a resonance form of pyridoquinazolinone **2.41**. Literature precedent exists for this type of reaction and the products have been isolated and shown to be stable,[89] although no attempt was made to isolate pyridoquinazolinone **2.41** in this example. Other side reactions appear to have occurred based on the ^{1}H NMR of the crude material but it is not clear what these are.



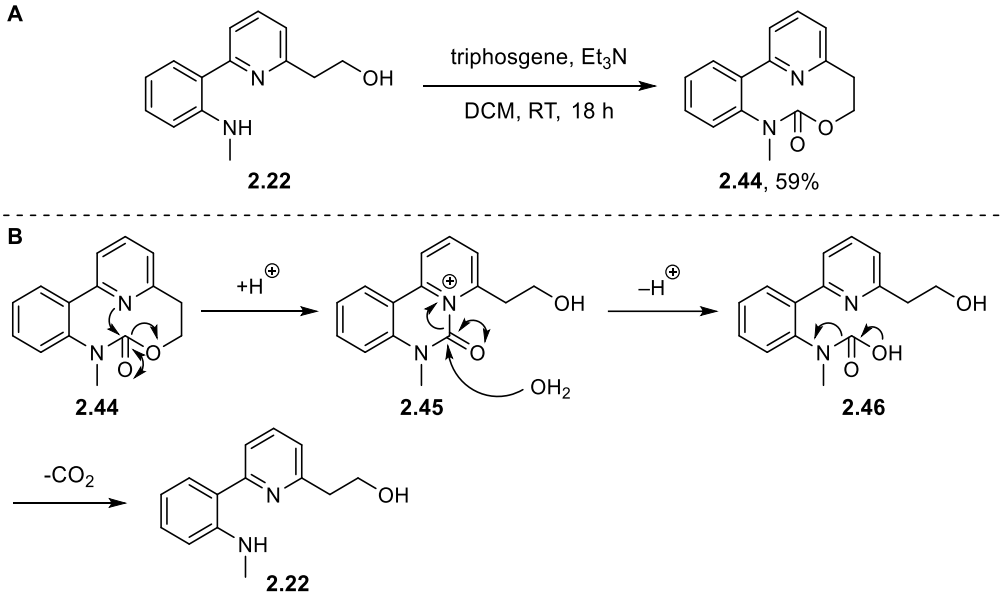
Scheme 50. [A] CRE cascade reaction using triphosgene. [B] Possible unwanted side reaction.

The CRE cascade reaction was also attempted using oxalyl chloride (Scheme 51). Unfortunately, this reaction also gave no desired product, possibly due to the potential formation of an isocyanate intermediate. It is also possible that the primary aniline is not suitable, due to the potential for the reaction with two equivalents of the electrophilic species giving undesired side products.



Scheme 51. CRE cascade reaction using oxalyl chloride

Next, the CRE cascade reaction was attempted with secondary amine **2.22** using triphosgene (Scheme 52A) and pleasingly the desired product **2.44** was observed in the ^{1}H NMR of the crude mixture. There was no evidence of precursor **2.22** remaining, however after purification by column chromatography (1:1 hexane:ethyl acetate) the product was obtained as a 1 : 0.13 mixture of product **2.44** : precursor **2.22**, suggesting that the product partially decomposed back to starting material on the column. A proposed mechanism for this decomposition is given in Scheme 52B. One possible cause of this decomposition could be the weakly acidic nature of the silica gel used in column chromatography, therefore 5% triethylamine was incorporated into the eluent system to ensure basic conditions. With this change in place no decomposition was observed, and the 10-membered carbamate **2.44** was obtained in 59% yield.

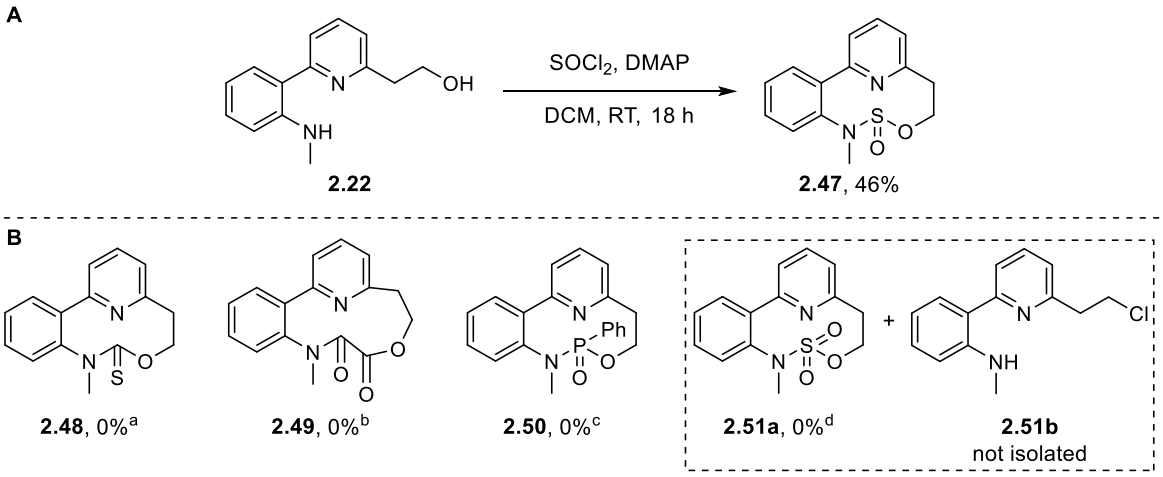


Scheme 52. [A] CRE cascade reaction using triphosgene. [B] Proposed mechanism for decomposition on silica gel.

The CRE cascade reaction was also successful when thionyl chloride was employed as the electrophile (Scheme 53A). This gave the 10-membered cyclic sulfuramidite **2.47** in 46% yield which appeared to be a single diastereoisomer, with the biaryl C–C bond, assumed to be a chiral axis based on previous work,[75] and the sulfur atom a stereogenic centre. The relative configuration of this diastereoisomer was not identified as the product was an oil which prevented X-ray crystallography.

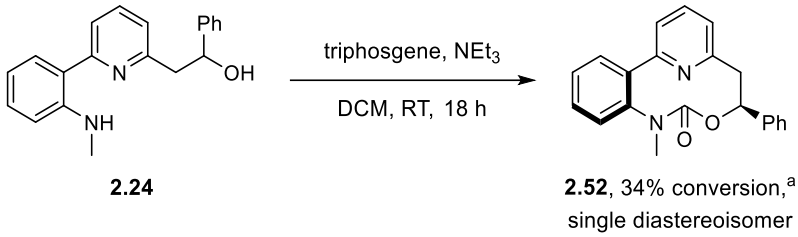
The CRE cascade reaction using a further four electrophilic reagents (thiophosgene, oxalyl chloride, phenylphosphonic dichloride and sulfuryl dichloride) were also attempted,

although all were unsuccessful (Scheme 53B). It is unclear why the reactions did not work, with the mass spectra and ^{1}H NMR spectra of the crude materials appearing to contain a large number of unidentifiable components, suggesting many side reactions took place. In the reaction with sulfuryl dichloride, one side reaction was identified which involved conversion of the alcohol into a chloride, with the chlorinated product **2.51b** being observed by mass spectrometry of the crude reaction mixture. This type of reaction is not unsurprising and there have been similar reactions reported in the literature.[90,91]



Scheme 53. [A] Successful CRE cascade reaction using thionyl chloride. [B] Unsuccessful CRE cascade reactions using thiophosgene, oxalyl chloride, phenylphosphonic dichloride and sulfuryl dichloride as electrophiles. Reaction conditions: [a] $CSCl_2$, DMAP, DCM, RT, 18 h. [b] $(COCl)_2$, Et_3N, DCM, RT, 18 h. [c] $OPPhCl_2$, DMAP, DCM, RT, 18 h. [d] SO_2Cl_2, DMAP, DCM, RT, 18 h.

The CRE cascade reaction was also attempted using the chiral secondary alcohol **2.24** (Scheme 54). Using triphosgene gave 10-membered carbamate **2.52** which contains two chiral units, a chiral biaryl axis and the point stereogenic centre, and so could potentially form two diastereoisomers. From the ^{1}H NMR of the crude reaction mixture the product appeared to have formed as a single diastereoisomer. The relative configuration was not experimentally determined but is likely as shown in Scheme 54, based on the selectivity seen in the Unsworth's groups previous atroposelective CRE cascade reactions.[75] Attempts to purify carbamate **2.52** were unsuccessful with significant degradation back to precursor **2.24** occurring during column chromatography, presumably by hydrolysis. The conversion was therefore determined by ^{1}H NMR by adding an internal standard to the crude reaction mixture. As the conversion was found to be relatively poor (34%) further attempts to purify this product were not performed.

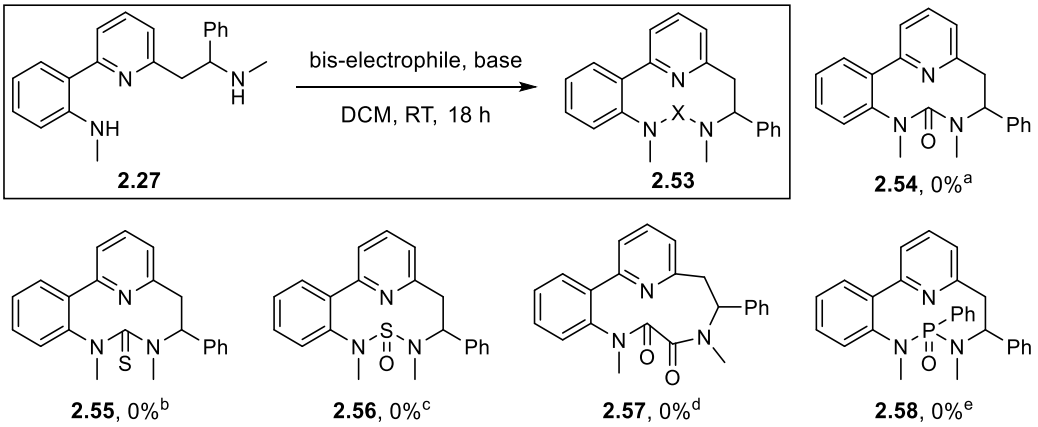


2.24

2.52, 34% conversion,[a] single diastereoisomer

Scheme 54. Atroposelective CRE cascade reaction using triphosgene. [a] Conversion measured by ^{1}H NMR of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard.

The CRE cascade reaction was then attempted using diamine precursor **2.27** with the expectation that the products would be less prone to degradation (Scheme 55). In all five of these reactions none of the desired medium-sized rings were isolated. As with the previous unsuccessful attempts it is unclear why these reactions were unsuccessful; in all cases a large mixture of products was observed with no clear major products forming. This makes it difficult to identify why the reactions failed, however, one possibility is that the aliphatic amine is too reactive, leading to undesired side reactions.



2.27

2.53

2.54, 0%[a]

2.55, 0%[b]

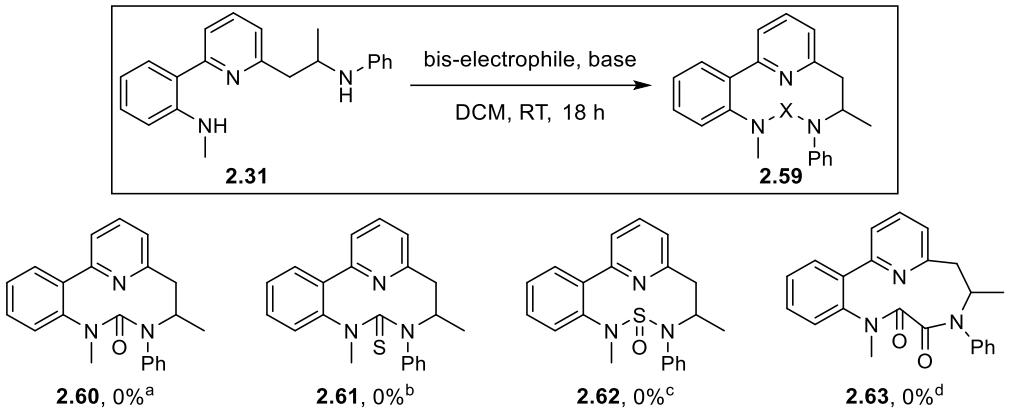
2.56, 0%[c]

2.57, 0%[d]

2.58, 0%[e]

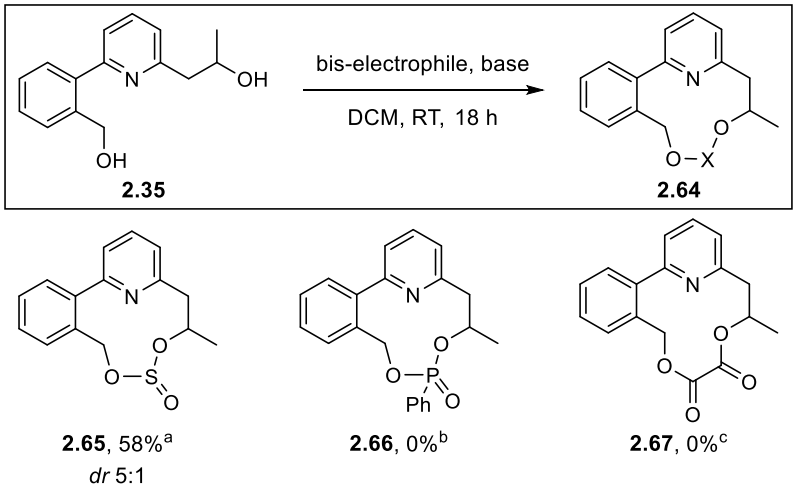
Scheme 55. Attempted CRE cascade reactions using a diamine precursor. Electrophile/base: [a] triphosgene, Et_3N. [b] $CSCl_2$, DMAP. [c] $SOCl_2$, DMAP. [d] $(COCl)_2$, Et_3N. [e] $OPPhCl_2$, DMAP

With this in mind, the CRE cascade reaction of bis-aniline **2.31** was attempted with the hope that a less reactive amine would result in fewer side reactions (Scheme 56). Unfortunately, all attempts were unsuccessful with the reason for this being unclear. In all cases there were no clearly identifiable major products; instead, it appears that many side reactions are taking place, giving a large number of side products.



Scheme 56. Attempted CRE cascade reaction using a bis-aniline precursor. Electrophile/base: [a] triphosgene, Et_3N. [b] $CSCl_2$, DMAP. [c] $SOCl_2$, DMAP. [d] $(COCl)_2$, Et_3N.

The CRE cascade reaction of diol **2.35** was attempted using thionyl chloride which gave the desired 11-membered sulfite ester **2.65** in 58% yield as a 5:1 mixture of diastereoisomers (Scheme 57). Product **2.65** contains two stereogenic centers as well as a chiral axis which means there are four potential diastereoisomers, but it is not clear which two diastereoisomers form during the reaction or what the major diastereoisomer is. The CRE cascade reaction using phenylphosphonic dichloride and oxalyl chloride, to give products **2.66** and **2.67**, were unsuccessful with no major side products able to be identified or isolated.

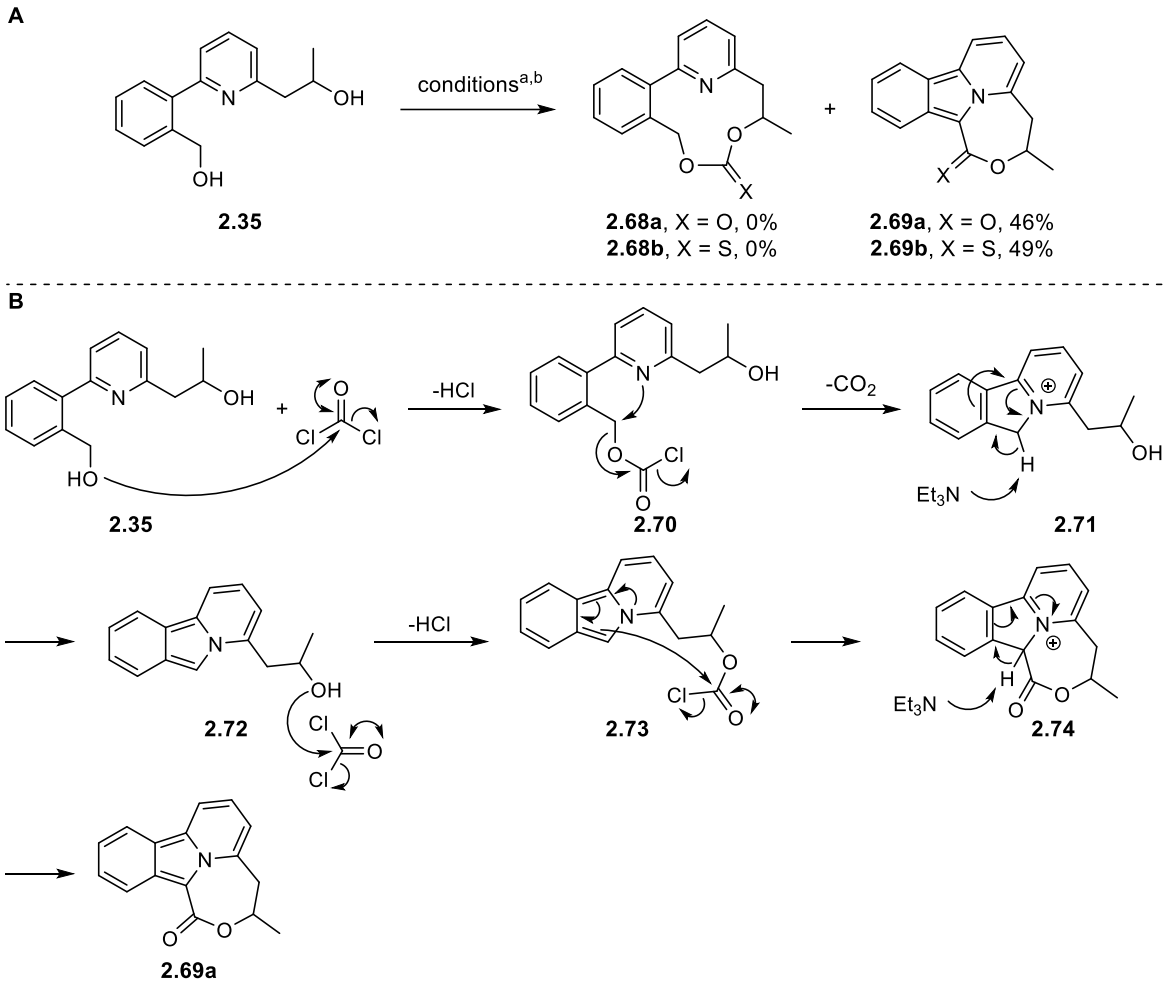


Scheme 57. CRE cascade reactions using a diol precursor. Electrophile/base: [a] $SOCl_2$, DMAP. [b] $OPPhCl_2$, DMAP. [c] $(COCl)_2$, Et_3N.

When the CRE cascade reaction of diol **2.35** was attempted with triphosgene and thiophosgene the desired 11-membered rings **2.68a** and **2.68b** were not formed. In both reactions an unexpected side reaction was observed, which gave lactone **2.69a** or thiolactone **2.69b** in 46% and 49% yield respectively (Scheme 58A). In the case of lactone

2.69a, a crystal was grown and an X-ray crystal structure was obtained to definitively confirm its structure (Figure 4).

A mechanism was proposed for the formation of these unexpected products (Scheme 58B), which starts with the attack of primary alcohol **2.35** into phosgene to give chloroformate **2.70**, in the manner anticipated for the planned CRE cascade reaction. Then, it is proposed that the pyridine nitrogen attacks the sp^3 carbon atom, liberating CO_2 and forming the 5-membered pyridinium **2.71**. This can then be deprotonated to neutralise the positive charge and form isoindole **2.72**. The alcohol of **2.72** can then attack another molecule of phosgene forming chloroformate **2.73**, the nitrogen of which can then promote attack of this chloroformate through the C–C double bond forming pyridinium **2.74**. A final deprotonation causes rearomatisation and forms the observed side product **2.69a**. As this proposed mechanism results in the consumption of 2 equivalents of phosgene/thiophosgene to form **2.69a**/**2.69b**, higher yields of these unusual side products could be achieved by increasing the equivalents of these reagents.



Scheme 58. [A] CRE cascade reactions using triphosgene and thiophosgene. Reaction conditions: [a] triphosgene, DMAP, DCM, RT, 18 h. [b] $CSCl_2$, DMAP, DCM, RT, 18 h. [B] Proposed mechanism for the formation of the isolated side product.

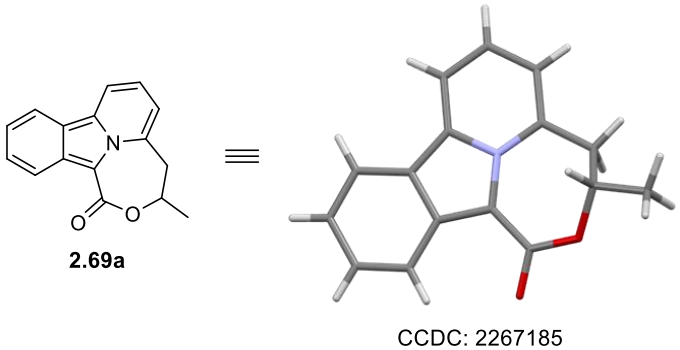
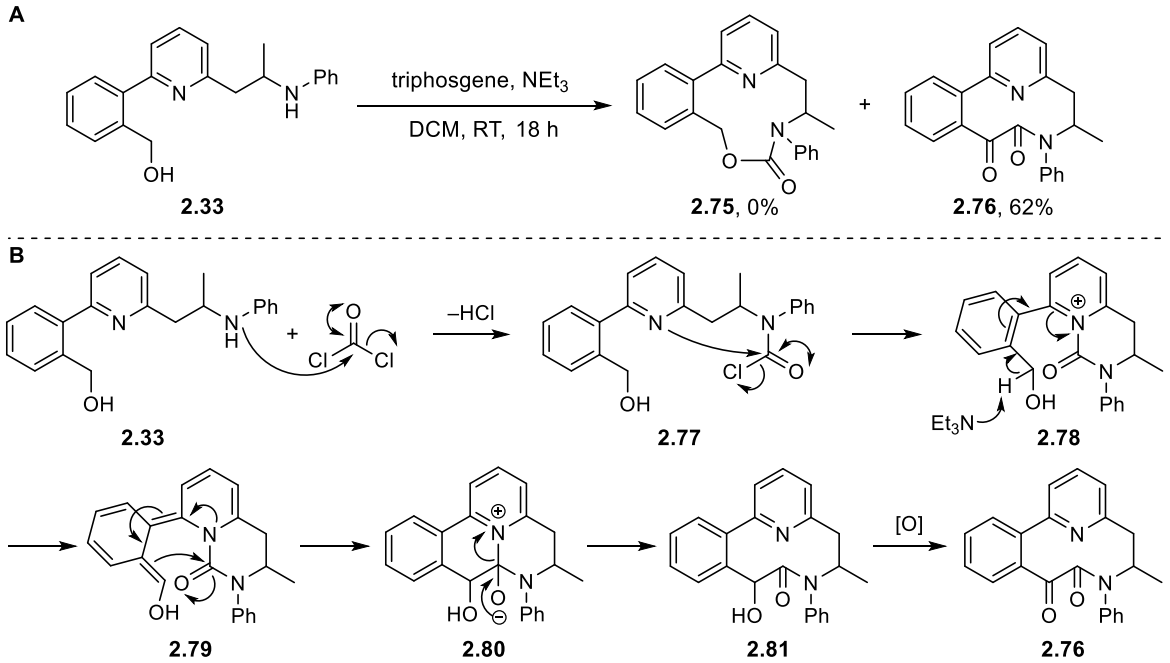


Figure 4. X-ray crystal structure of side product **2.69a**.

Since the CRE cascade reaction starting from the primary alcohol end of diol **2.35** led to unwanted side products, it was thought that if the reaction started at the opposite end, the planned CRE cascade reaction would be more likely to take place. Therefore, the CRE cascade reaction was attempted using amino alcohol **2.33** where the aniline is likely

more nucleophilic and hence the triphoshgene should add to this end first. Unfortunately, when reacted with triphosgene, there was no evidence for the formation of the desired 11-membered carbamate **2.75**. Instead, another unexpected side product was obtained, which was assigned to be the 10-membered ring **2.76** which was isolated in 62% yield (Scheme 59A).

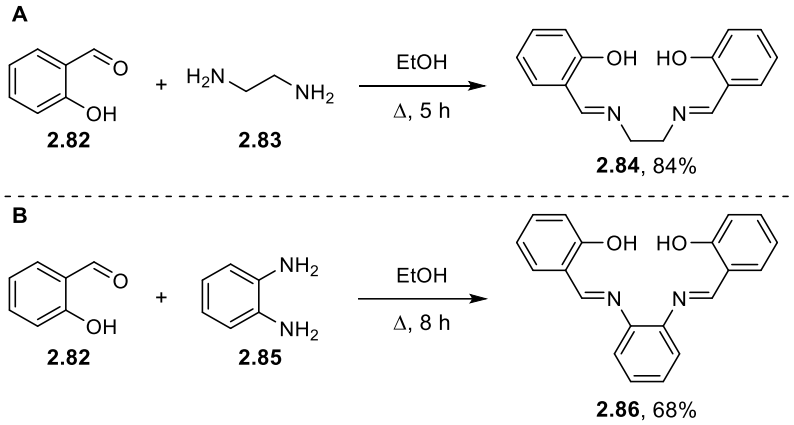
A mechanism was proposed for the formation of this side product (Scheme 59B), which starts with the attack of the aniline **2.33** into phosgene giving carbamoyl chloride **2.77**. The pyridine can then attack into the carbonyl forming the 6-membered ring **2.78**. This intermediate can then be deprotonated, neutralising the positive charge, and forming the enamine like structure **2.79**. Attack through the double bond, into the carbonyl, leads to the bicyclic structure **2.80** which then fragments into the 10-membered ring **2.81**. If this alcohol is oxidised to the ketone (the oxidant is unknown – potential aerobic oxidation), structure **2.76** is obtained which was tentatively assigned using the NMR, mass spectrometry and IR data collected. X-ray diffraction could be used to definitively assign the structure of **2.76**, although all attempts at growing a crystal were unsuccessful.



Scheme 59. [A] CRE cascade reaction of an amino alcohol precursor using triphosgene. [B] Proposed mechanism for the formation of a side product.

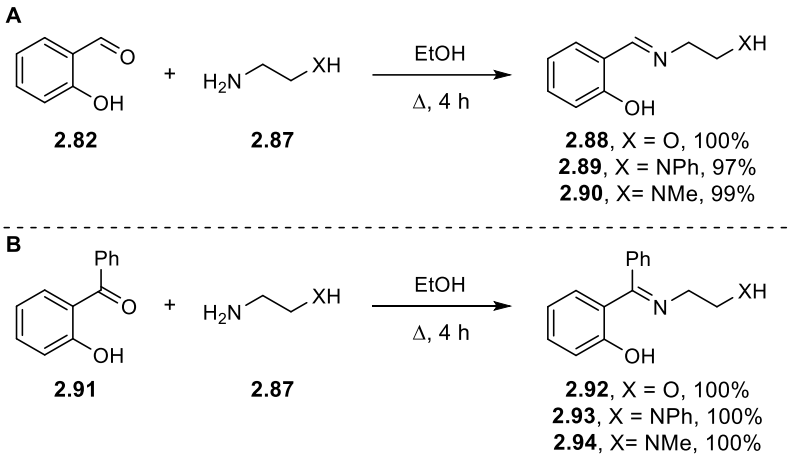
2.4 Synthesis of Precursors Containing Imines as the Internal Nucleophile

There are three main types of internal nucleophiles that have been commonly used in the CRE cascade reactions within the Unsworth group: sulfides, pyridines and tertiary amines. For the CRE strategy to work the internal nucleophile must be fully saturated *i.e.*, not contain any bonds to hydrogen, to preclude the reactive intermediate undergoing deprotonation to form a stable, neutral species. An interesting internal nucleophile that has not been tested before is the imine functionality. Two precursors based on salen-type ligands were initially synthesised by the condensation reaction of salicylaldehyde **2.82** with aliphatic diamine **2.83** or aromatic diamine **2.85** (Scheme 60). This gave the desired precursors **2.84** and **2.86**, which contain two imine internal nucleophiles, in 84% and 68% yield respectively.



Scheme 60. Synthesis of two precursors containing two imines as the internal nucleophiles.

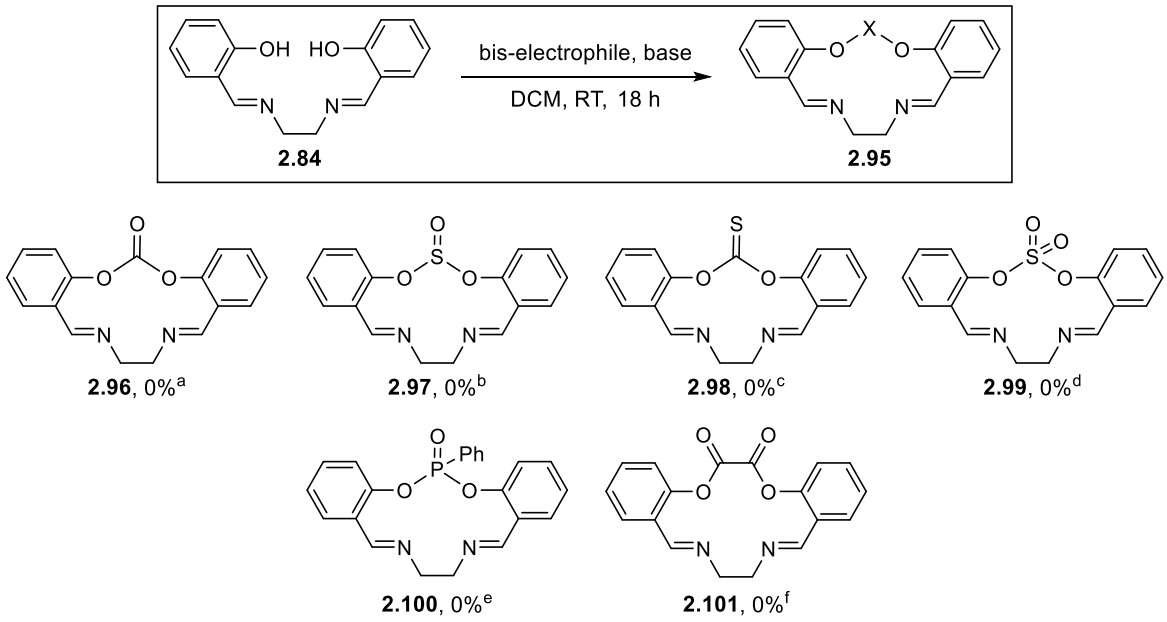
A series of precursors containing a single imine as the internal nucleophile were also synthesised. Three were made from the condensation reaction of aldehyde **2.82** with amines **2.87** to give the imines **2.88**–**2.90** (Scheme 61A), each of which has a different terminal nucleophile: alcohol (**2.88**), aniline (**2.89**) or aliphatic amine (**2.90**). Three more precursors were made from the condensation of ketone **2.91** with amines **2.87** to give imines **2.92**–**2.94**, again with three different terminal nucleophiles (Scheme 61B). In all six cases, condensation proceeded quantitatively without the need for purification by column chromatography.



Scheme 61. Synthesis of precursors containing a single imine internal nucleophile.

2.5 Cyclisation/Ring Expansion Cascade Reactions of Imine Containing Precursors

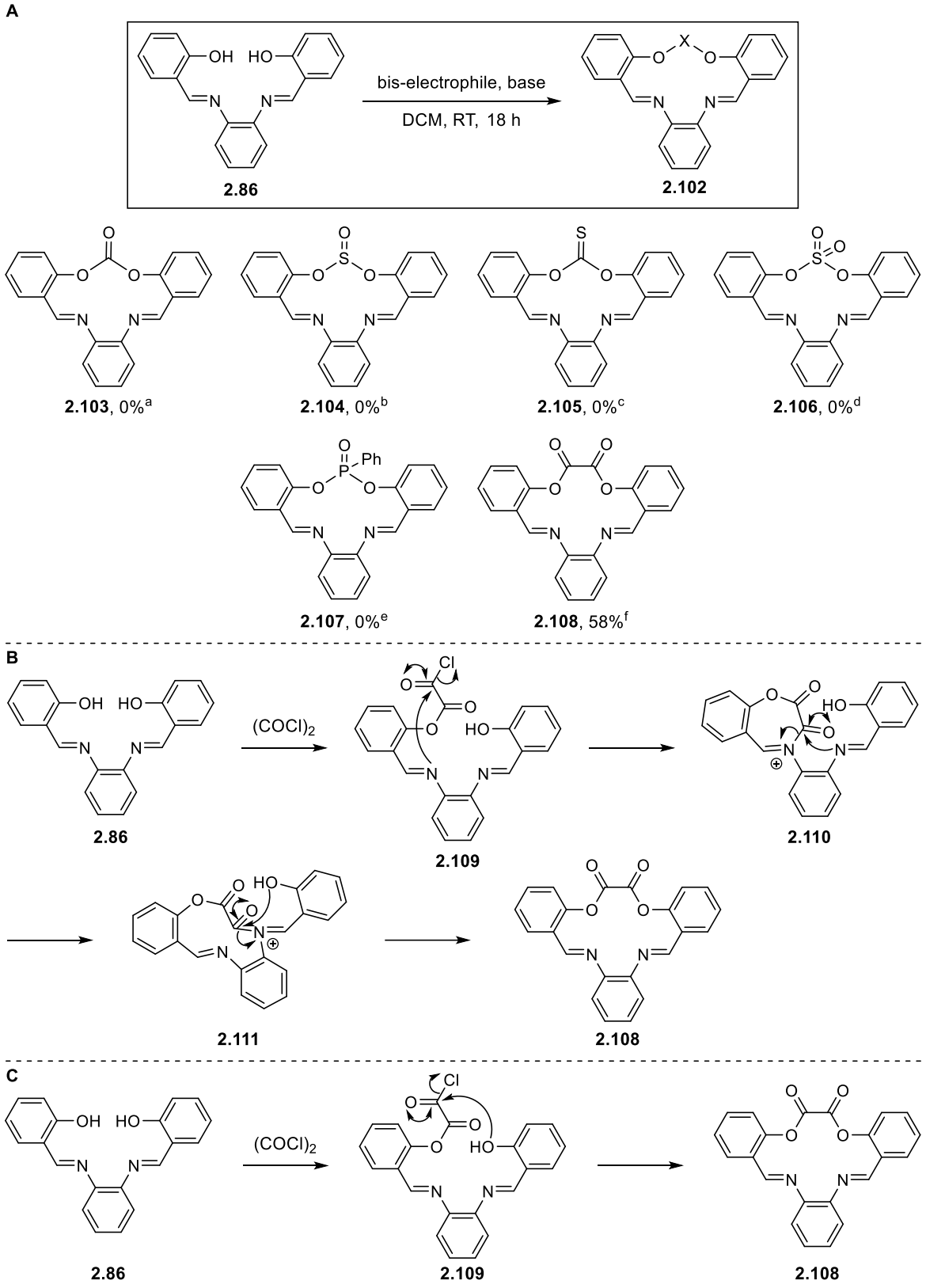
The CRE cascade reaction was first attempted using precursor **2.84** with six different electrophiles (Scheme 62). Unfortunately, all attempts were unsuccessful with all reactions a giving a range of side products that could not be identified. Very similar reactions have been reported before using phosphoryl dichlorides, although the conditions for the CRE cascade reactions varied slightly from the literature.[92] It was therefore surprising that the reaction with phenylphosphonic dichloride, to form product **2.100**, was unsuccessful when the literature appeared to suggest this product could be obtained in high yield. To verify whether the differing conditions were problematic, one of the reactions presented in the literature was attempted following their procedure exactly, and while the authors reported a 74% yield, this could not be replicated and in fact, no products were isolated.



Scheme 62. Attempted CRE cascade reactions using an imine containing precursor. Electrophile/base: [a] triphosgene, Et_3N. [b] $SOCl_2$, DMAP. [c] $CSCl_2$, DMAP. [d] SO_2Cl_2, DMAP. [e] $OPPhCl_2$, DMAP. [f] $(COCl)_2$, Et_3N.

The CRE cascade reactions were then attempted on precursor **2.86** using the six different electrophiles (Scheme 63A). The first five electrophiles that were attempted failed to yield any desired products **2.103**–**2.107** and similar to the previous attempts they all produced a large mixture of unidentifiable side products. The reaction with oxalyl chloride was however successful and oxalate **2.108** was observed by mass spectrometry, ^1H and ^{13}C NMR spectroscopy of the crude mixture. This product was found to be unstable and decomposed to diol **2.86** when column chromatography was attempted, when left in solution overnight or under aqueous conditions (e.g. during aqueous work-up). Ultimately the product was purified using a silica plug in order to minimise the time the compound spent on the silica, giving oxalate **2.108** in 58% yield with no signs of decomposition in the ^1H NMR spectrum.

Whilst this would be a good yield for a CRE cascade reaction, based on the unsuccessful nature of the other reaction attempts on this substrate **2.86** and the previous **2.84**, it is not convincing that this proceeds *via* a CRE cascade mechanism (Scheme 63B). An alternative explanation for this result is that the precursor **2.86** is preorganised for cyclisation due to the highly conjugated nature of starting material **2.86**. The two alcohol groups may be held close together which facilitates a direct end-to-end cyclisation with the imines playing no part in this (Scheme 63C). Therefore, a more convincing example of an imine acting as an internal nucleophile was required.



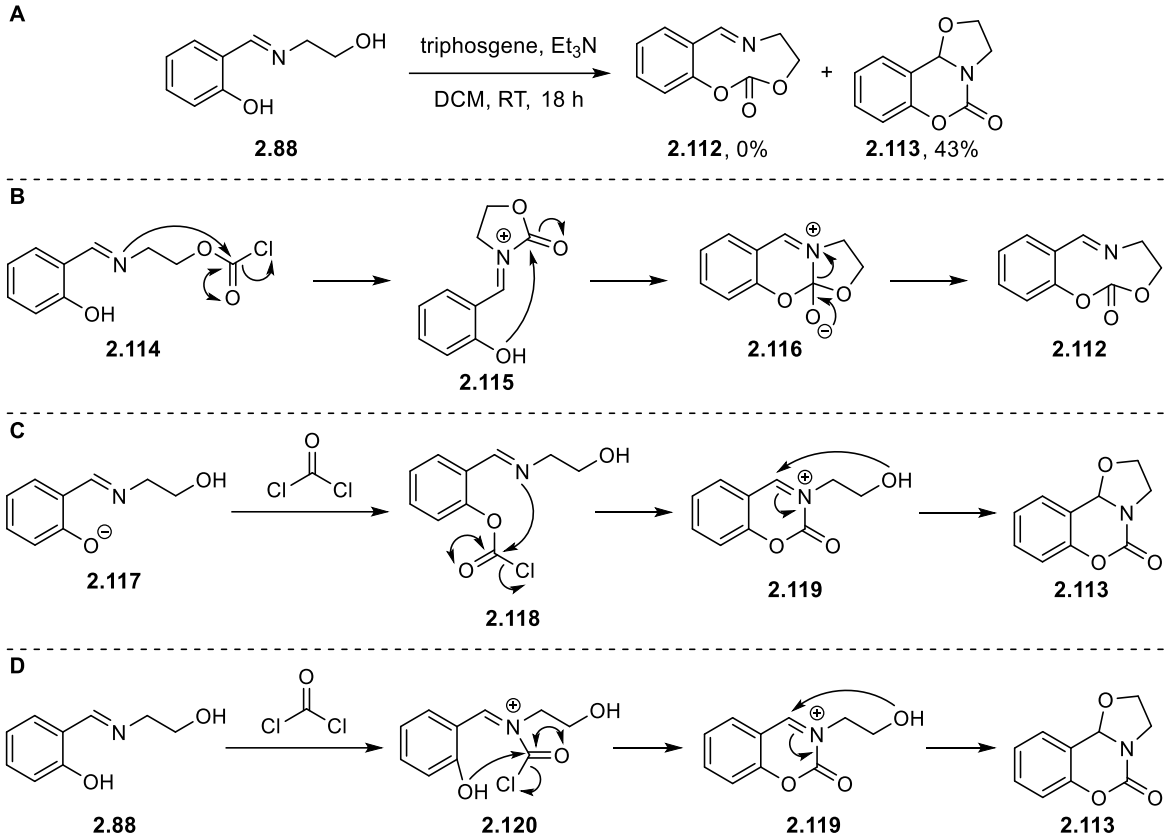
Scheme 63. [A] Attempted CRE cascade reactions using an imine containing precursor. Electrophile/base: [a] triphosgene, Et_3N. [b] $SOCl_2$, DMAP. [c] $CSCl_2$, DMAP. [d] SO_2Cl_2, DMAP. [e] $OPPhCl_2$, DMAP. [f] $(COCl)_2$, Et_3N. [B] CRE cascade mechanism. [C] Direct end-to-end cyclisation mechanism.

Imine **2.88** was chosen as the next precursor for the CRE cascade reaction to be attempted on. This was done using triphosgene as the electrophile (Scheme 64A) and disappointingly there was no evidence of the desired medium-sized cyclic carbonate **2.112** in the ^{1}H NMR of the crude mixture. In this case a clear side product had formed and was identified as carbamate **2.113** which was isolated in 43% yield. This was quite unexpected based on the initially proposed mechanism for this reaction (Scheme 64B). We initially thought the aliphatic alcohol would be more nucleophilic than the phenol and therefore the triphosgene would first add to this more nucleophilic alcohol to give chloroformate **2.114**. The imine could then attack this chloroformate forming acyliminium **2.115**. At this point there are two possibilities, first is the phenol attacks the iminium, however this would form a highly strained four-membered ring which would be very unfavourable. Second and more likely, is the phenol attacks the carbonyl forming the fused five-membered intermediate **2.116** which can then fragment to give the desired medium-sized ring **2.112**.

This mechanism did not explain the formation of the side product and therefore a new mechanism was proposed (Scheme 64C). Comparing the pK_a of triethylamine (conjugate acid pK_a ca. 11) with a typical phenol (pK_a ca. 10), it is reasonable to think that triethylamine would deprotonate phenol **2.88** to give phenoxide **2.117**. This phenoxide may be more nucleophilic than the aliphatic alcohol and therefore explain why the triphosgene may preferentially add to this group, forming chloroformate **2.118**. Next, the imine would attack into the carbonyl forming acyliminium **2.119**. This intermediate again contains two electrophilic sites, the iminium and the carbonyl, however attack of the alcohol into either of these sites would proceed through 5-membered transition states. It is likely that the iminium is more electrophilic than the carbonyl and therefore the alcohol preferentially attacks this site forming the observed product **2.113**.

Based on the assumption that triethylamine was deprotonating the phenol, the reaction was attempted without any base present in the hope that if both alcohols are protonated, the aliphatic alcohol should be more nucleophilic and therefore react *via* the mechanism outlined in Scheme 64B to give the desired medium-sized ring. Unfortunately, this made no difference to the outcome of the reaction, with the major product being carbamate **2.113** and no evidence of the desired medium-sized ring **2.112**. Another possibility is that the imine is the most nucleophilic group which leads to acylation at this position first to give acyl iminium **2.120** (Scheme 64D). The phenol can then attack into the

carbonyl leading to carbamate **2.119** and again the aliphatic alcohol can attack into the iminium to give the side product **2.113**.

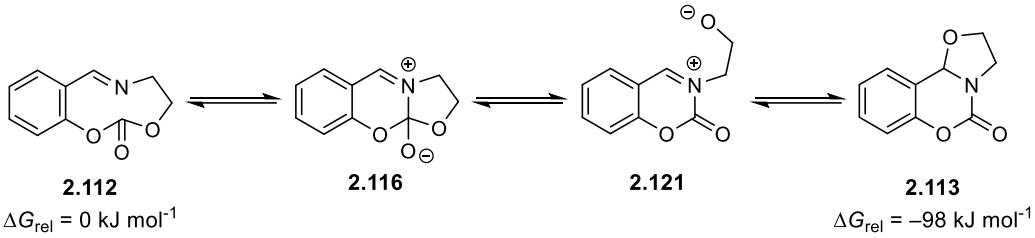


Scheme 64. [A] Attempted CRE cascade reaction with an imine internal nucleophile. [B] Initially expected mechanism yielding the desired medium-sized ring. [C] Proposed mechanism to explain the formation of the side product. [D] Alternative mechanism explaining the formation of the side product.

Another possibility is that the steps involved in the mechanism of this reaction are reversible and exist in equilibrium (Scheme 65). In this case the phosgene could add to the aliphatic alcohol first and follow the pathway shown in Scheme 64B to give 9-membered ring **2.112**. The imine may then be able to attack back into the carbonyl reforming intermediate **2.116**. Alkoxide **2.121** may then form which can attack the iminium forming the observed product **2.113**. Although this pathway may be less favourable, due to the alkoxide being a worse leaving group than the iminium, carbamate **2.113** may build up over the course of the reaction if there is sufficient thermodynamic driving force *i.e.*, structure **2.113** is much lower in energy then structure **2.112**.

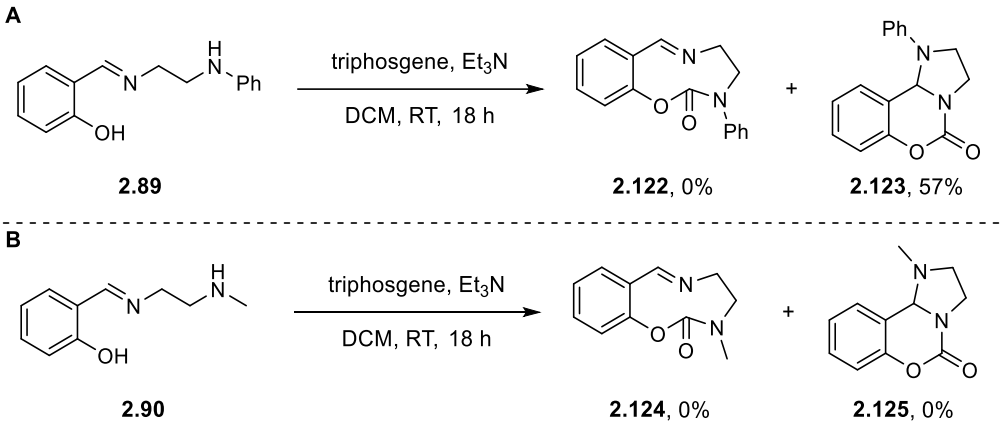
This energy difference between structures **2.112** and **2.113** was probed using Density Functional Theory (DFT) calculations. Initially, conformational analysis was performed to obtain the lowest energy structures of both **2.112** and **2.113**. The structures

obtained from this were retained and optimised at the B3LYP/6-31G* level of theory in vacuum. The lowest energy structure of each compound was then fully optimised with tight convergence criteria, using the same B3LYP/6-31G* level of theory, with frequency calculations to obtain their thermodynamic parameters. The results of these calculations showed that structure **2.113** was 98 kJ mol^{-1} lower in Gibbs free energy than structure **2.112**. Based on this difference it is expected that if these isomers are indeed in equilibrium, the equilibrium would lie entirely towards structure **2.113**.



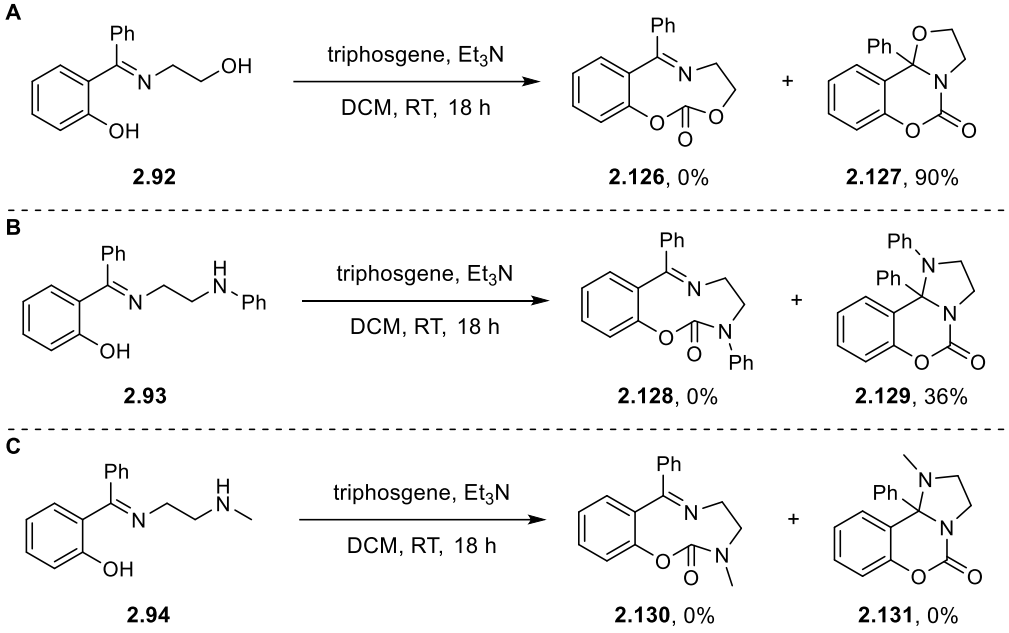
Scheme 65. Possible equilibrium that could lead to the formation of carbamate **2.113**. ΔG_{rel} values were calculated at the B3LYP/6-31G* level of theory in vacuum.

The CRE cascade reaction was next attempted using precursors **2.89** and **2.90** which contain an aniline or aliphatic amine nucleophile (Scheme 66). The expectation in these cases was that the aniline/aliphatic amine would be the most nucleophilic group and react with the triphosgene electrophile first, which would lead to the formation of the desired 9-membered ring. In the case of aniline **2.89** this did not occur, instead the tricyclic structure **2.123** was the major product, as was the case in the previous example. The aliphatic amine precursor **2.90** was also unsuccessful with a range of unidentified side products forming in the reaction.



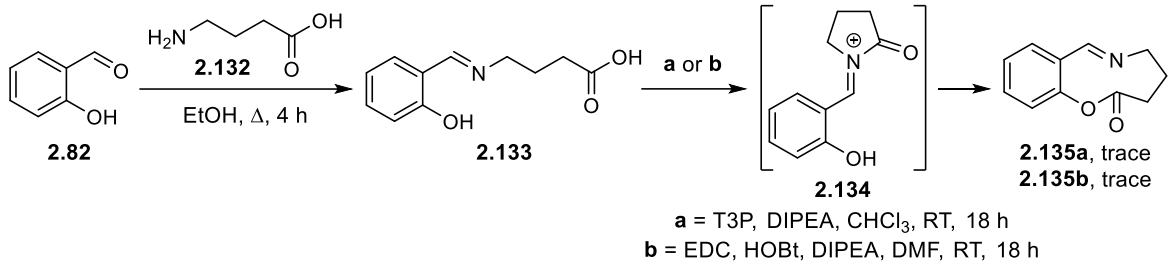
Scheme 66. [A] Attempted CRE cascade reaction using an imine internal nucleophile with an aniline terminal nucleophile. [B] Attempted CRE cascade reaction using an imine internal nucleophile with an aliphatic amine terminal nucleophile.

In an attempt to prevent attack into the iminium intermediate, precursors **2.92**–**2.94** were used which have an added phenyl group (Scheme 67). It was hoped that this added steric bulk would hinder attack into the iminium intermediate and thus favour the formation of the desired 9-memebered rings. This did not have the desired effect and in the case of alcohol **2.92** and aniline **2.93** the tricyclic structures **2.127** and **2.129** formed in 90% and 36% yield respectively, with no evidence for the formation of 9-membered rings **2.126** and **2.128**. Aliphatic amine **2.94** also failed to yield the desired medium-sized ring **2.130**, although the side products formed in this reaction were not identified.



Scheme 67. Attempted CRE cascade reactions using an imine internal nucleophile.

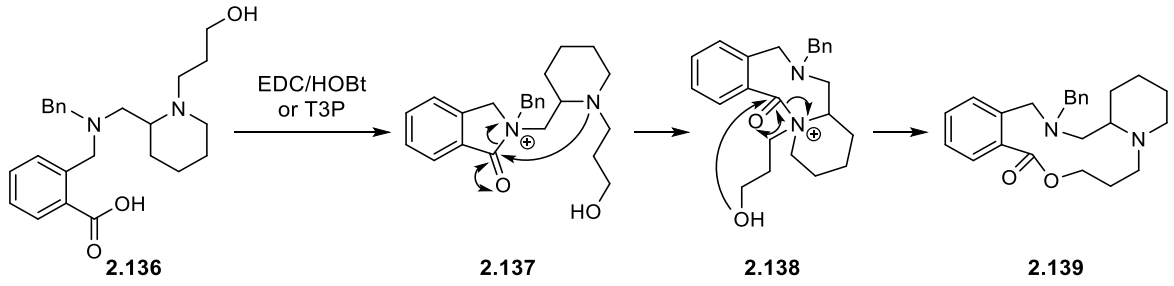
Finally, a CRE cascade reaction using an activated carboxylic acid electrophile was attempted (Scheme 68). In this case the cascade must start from the carboxylic acid and proceed *via* intermediate **2.134** which should prevent the formation of the tricyclic side product that was observed in the previous reactions. The condensation reaction of salicylaldehyde **2.82** and GABA **2.132** gave the imine **2.133**, although the reaction did not go to completion and small amounts of starting materials **2.82** and **2.132** were still present. Nevertheless, the CRE cascade reaction was attempted using EDC/HOBt or T3P as the coupling agent. In both cases product formation was observed by mass spectrometry although none of the 9-membered ring **2.135** could be isolated. It is not clear why this reaction did not work but it was apparent that imines are not suitable for the CRE cascade reaction and often led to the formation of unwanted side products.



Scheme 68. Attempted CRE cascade reaction with an imine internal nucleophile using an activated carboxylic acid electrophile.

2.6 Cyclisation/Ring Expansion Cascade of Precursors Containing Multiple Internal Nucleophiles Using Activated Carboxylic Acid Electrophiles

The use of multiple internal nucleophiles allows larger ring systems to be generated through longer cascade sequences. The first system to be investigated was that of carboxylic acid **2.136** (Scheme 69), which contains two tertiary amines that can act as internal nucleophiles and an alcohol to act as the terminal nucleophile. If successful, this would proceed through three "normal"-sized ring transition states to yield the 12-membered lactone **2.139**.

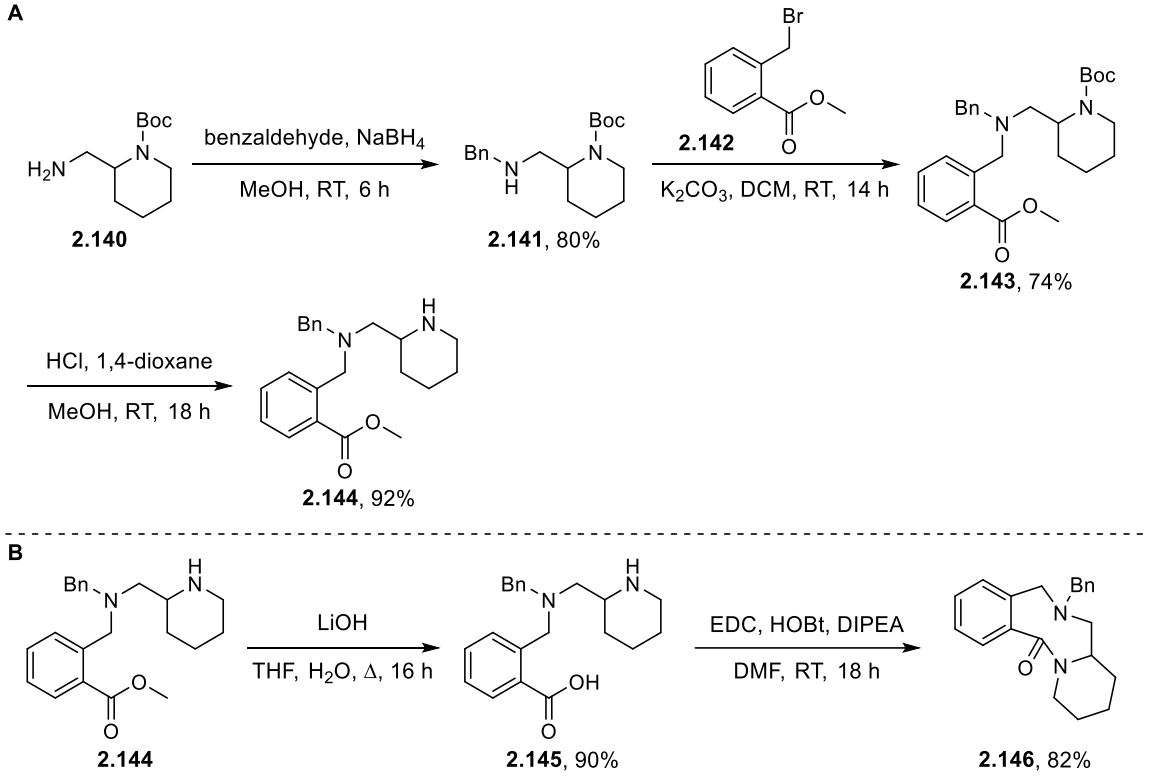


Scheme 69. Proposed CRE cascade reaction to give 12-membered lactone **2.139**.

The first step in the synthesis of acid **2.136** was the reductive amination of primary amine **2.140** with benzaldehyde. This gave secondary amine **2.141** in 80% yield which was alkylated with benzyl bromide **2.142** to give tertiary amine **2.143** in 74% yield. The Boc protecting group of amine **2.143** was then cleaved using hydrochloric acid to give secondary amine **2.144** in 92% yield (Scheme 70A).

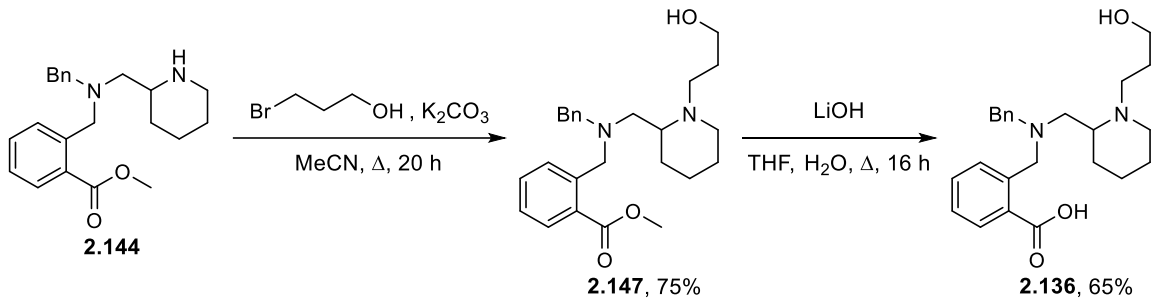
At this point it was realised that if methyl ester **2.144** was hydrolysed the product of this could be used in a CRE cascade reaction, based on a single internal nucleophile (Scheme 70B). This was therefore attempted, and methyl ester **2.144** was hydrolysed using lithium hydroxide to give the carboxylic acid **2.145**. The CRE cascade reaction was attempted using EDC and HOBt as coupling agents and pleasingly gave 8-membered lactam **2.146** in 82%

yield. This gave a good indication that both nitrogen atoms were able to act as nucleophiles which made the double internal nucleophile substrate look more promising.



Scheme 70. [A] First steps towards the synthesis of the precursor for a double internal nucleophile CRE cascade reaction. [B] Ester hydrolysis and subsequent CRE cascade reaction to form 8-membered lactam **2.146**.

The synthesis of the precursor for the double internal nucleophile CRE cascade reaction was completed by alkylating secondary amine **2.144** with 3-bromopropan-1-ol in a nucleophilic substitution reaction to give tertiary amine **2.147** in 75% yield. Methyl ester **2.147** was then hydrolysed using lithium hydroxide to give carboxylic acid **2.136**, the starting material for the CRE cascade reaction, in 65% yield (Scheme 71).

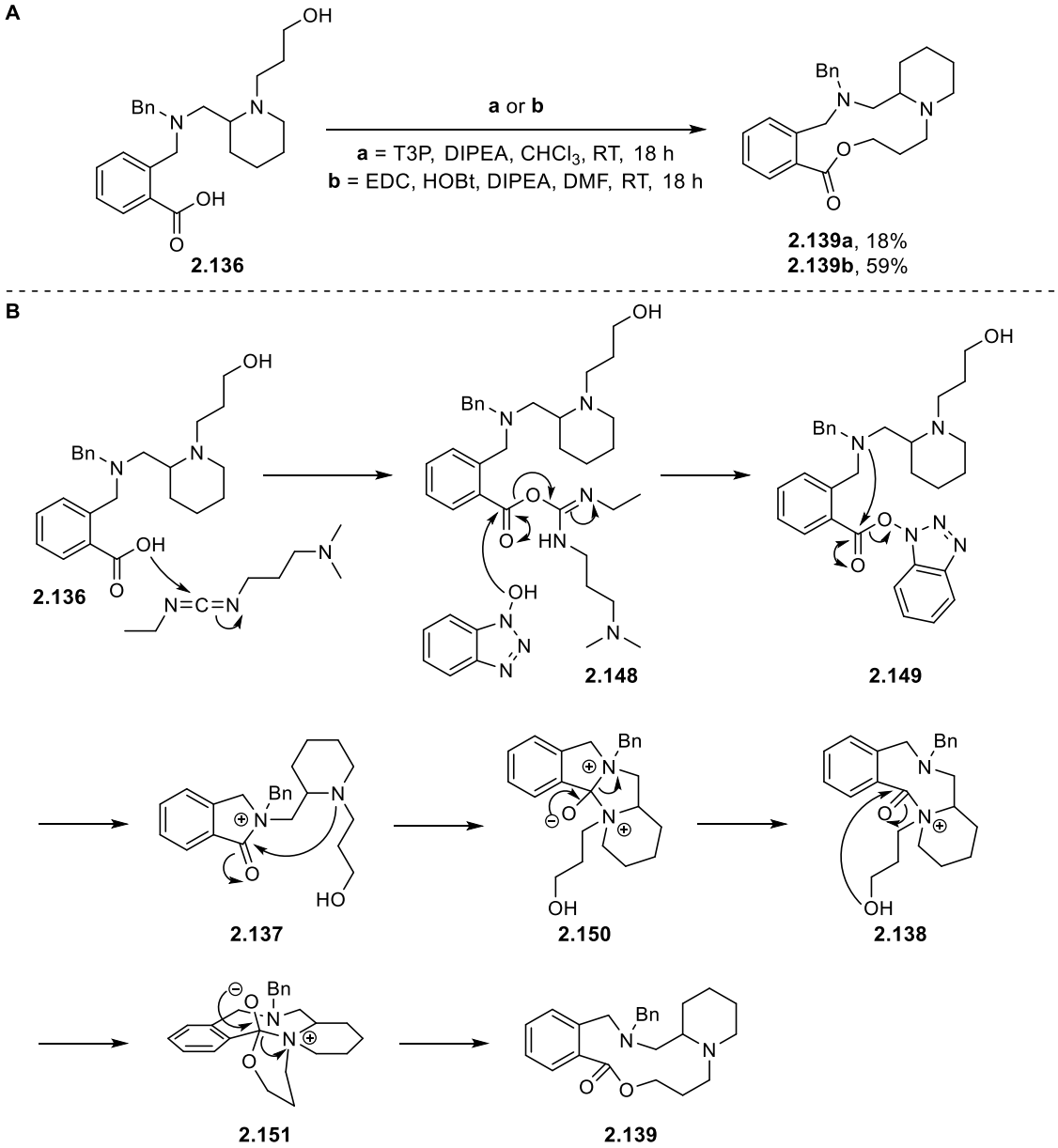


Scheme 71. Alkylation of secondary amine **2.144** and subsequent hydrolysis to give the CRE cascade reaction precursor.

With starting material **2.136** successfully synthesised the CRE cascade reaction was attempted using two different coupling agents: EDC/HOBt and T3P. In the case of T3P the 12-membered lactone **2.139a** was isolated, albeit in low yield of only 18% yield. Fortunately, using EDC and HOBt as coupling agents proved to be far more successful with the yield of the desired 12-membered lactone **2.139b** being 59% (Scheme 72A).

In the proposed mechanism (Scheme 72B) for this reaction the carboxylic acid is activated by first attacking into a molecule of EDC to form **2.148**, followed by HOBt attacking into the carbonyl forming activated ester **2.149**. Once activated the first tertiary amine can attack into the carbonyl forming 5-membered cyclic intermediate **2.137** and kicking out a HOBt anion which acts as a catalyst and can react again. Next, the second tertiary amine attacks the carbonyl forming the second 5-membered cyclic intermediate **2.150** which then fragments forming acyl ammonium **2.138**. Finally, the alcohol attacks the carbonyl forming the 6-membered cyclic intermediate **2.151** which undergoes fragmentation to give 12-membered lactone **2.139**, completing the cascade process.

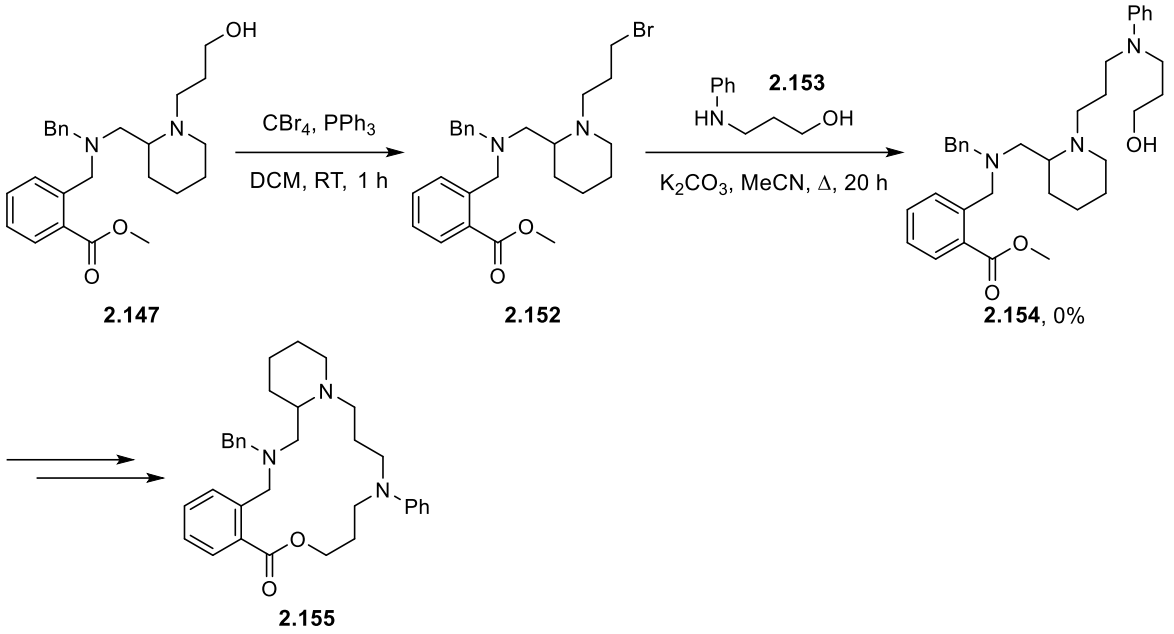
It is currently not fully understood why there is such large differences in yields between the two coupling conditions, but one possible factor is the choice of solvent. In the case of EDC/HOBt, DMF is used as the solvent which is more polar than chloroform which is used in the T3P conditions. This increased polarity could mean there are more favourable interactions between the solvent and the charged intermediates, possibly stabilising some of the transition states leading to a more favourable reaction. This is unlikely to be the only factor affecting the yields however, as the coupling agents themselves and by-products of the reactions are also different. In the EDC/HOBt conditions the main by-product is a neutral urea molecule whereas in the T3P conditions the main by-product is a charged phosphonic acid, this could potentially be interacting with the charged intermediates and influencing the reaction outcome.



Scheme 72. [A] Different coupling conditions used for the CRE cascade reaction. [B] Proposed mechanism for the CRE cascade reaction using EDC/HOBt as coupling agents.

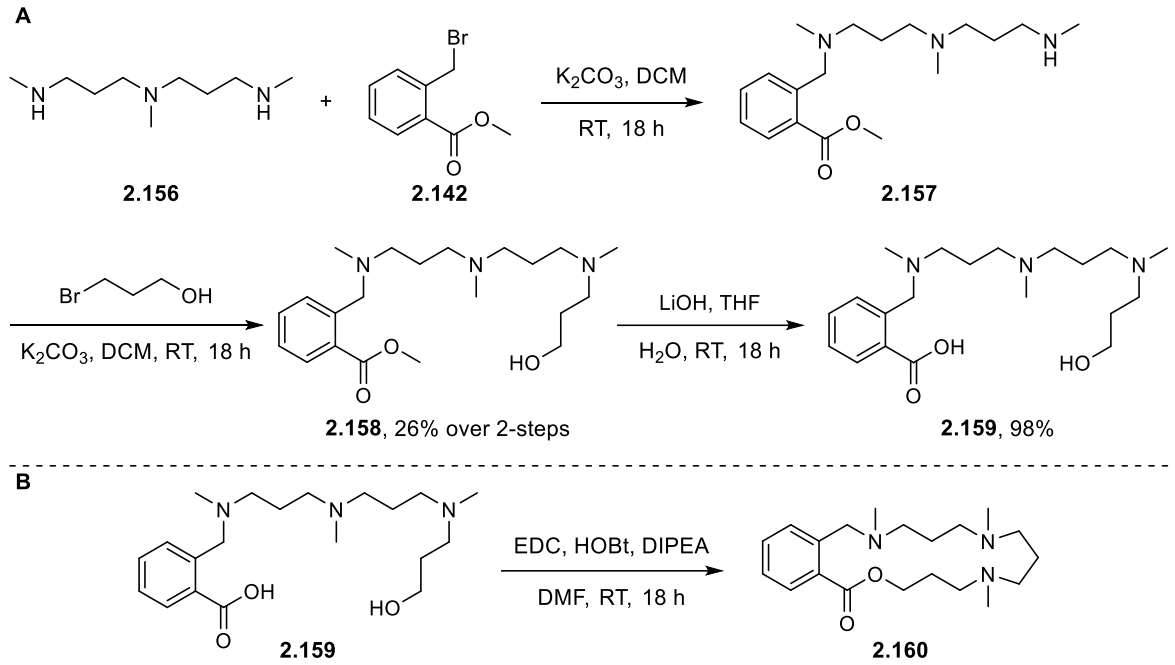
Having shown that this system works with two internal nucleophiles, it was thought that a CRE cascade reaction with three internal nucleophiles would be possible (Scheme 73). The Appel reaction using alcohol **2.147** gave alkyl bromide **2.152** although this could not be isolated as a pure compound and was found to contain minor unidentified impurities. Nucleophilic substitution with aniline **2.153** was attempted and although mass spectrometry showed evidence of product **2.154** formation, purification by column chromatography was challenging, with the product co-eluting with significant impurities

that were unidentified. This meant the CRE cascade reaction to give 16-membered lactone **2.155** could not be attempted.



Scheme 73. Attempted synthesis of a CRE cascade reaction precursor containing three internal nucleophiles.

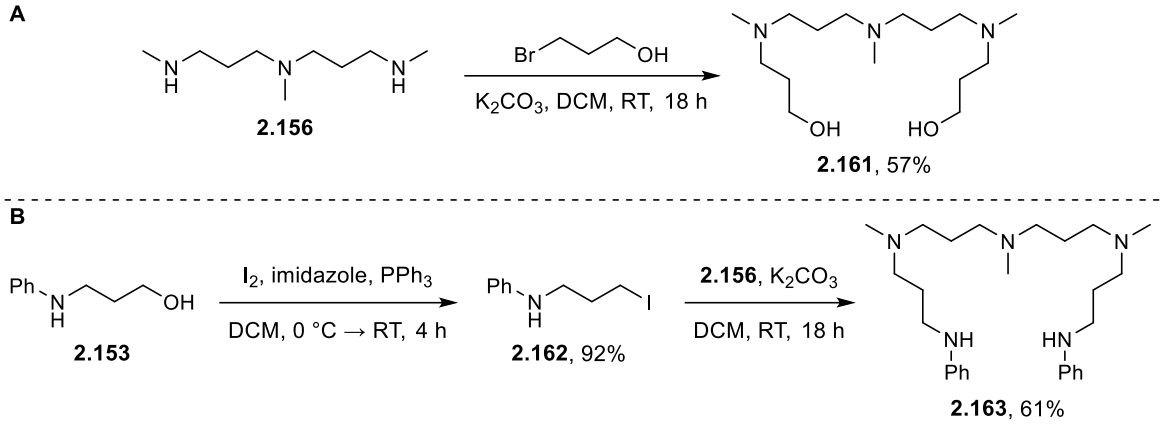
A second precursor containing three internal nucleophiles was synthesised successfully (Scheme 74A). This began with amine **2.156** which was alkylated using benzyl bromide **2.142** to give the monoalkylated product **2.157**. Alkylation using 3-bromo-1-propanol gave the amino ester **2.158** in 26% yield over both alkylation steps. Hydrolysis of ester **2.158** using lithium hydroxide gave amino acid **2.159** in 98% yield. The CRE cascade reaction was then attempted using EDC/HOBt as coupling agents and the major product was tentatively assigned to structure **2.160** based on mass spectrometry showing the correct mass and ^{1}H NMR that showed the OCH_2 protons were shifted downfield, which is consistent with the more strongly electron withdrawing ester in product **2.160**. Purification of product **2.160** by column chromatography was challenging due to the highly polar nature of product **2.160** and co-elution with unidentified side products occurred.



Scheme 74. [A] Synthesis of a CRE cascade reaction precursor containing three internal nucleophiles. [B] Attempted CRE cascade reaction where product formation was observed by ^{1}H NMR and mass spectrometry but purification was not possible.

2.7 Synthesis of Precursors for the Cyclisation/Ring Expansion Cascade Reaction with Multiple Internal Nucleophiles Using Bis-Electrophilic Reagents

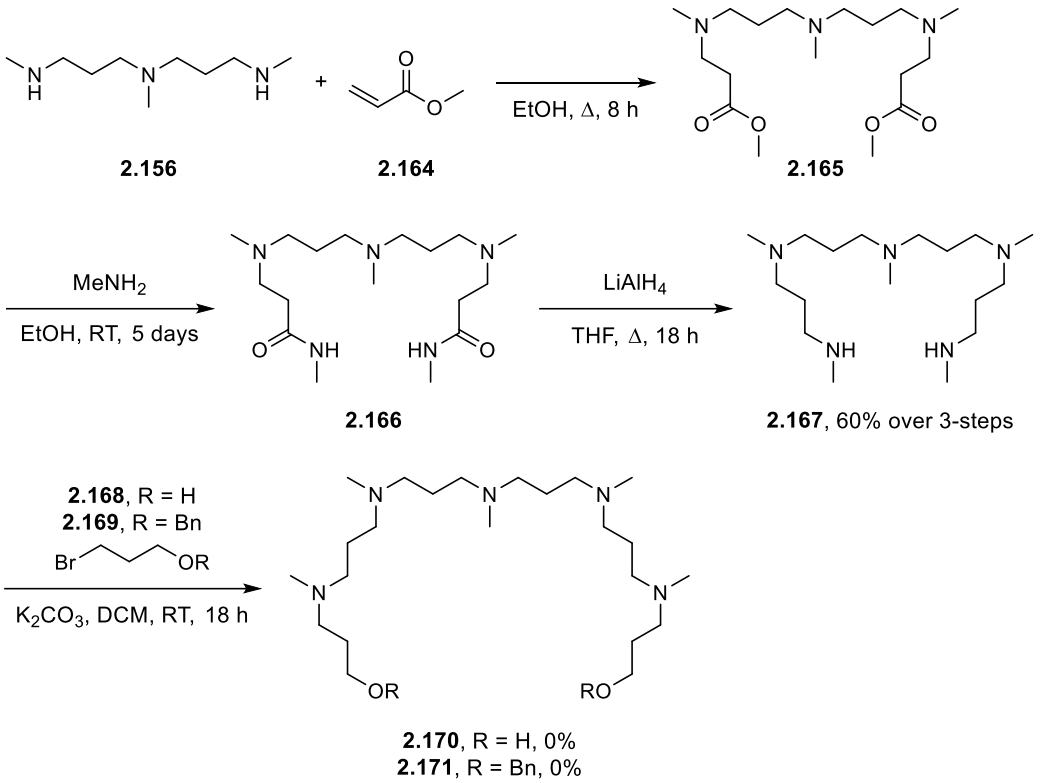
Two precursors were synthesised that contain three internal nucleophiles and two terminal nucleophiles so that they can be reacted with bis-electrophiles. The first of these was synthesised in one step by reacting amine **2.156** with an excess of 3-bromo-1-propanol to give the disubstituted product **2.161**, bearing two alcohol groups, in 57% yield (Scheme 75A). The second precursor was made by first converting alcohol **2.153** into iodide **2.162**, in 92% yield, then reacting this with amine **2.156** to give the disubstituted product **2.163**, bearing two aniline groups, in 61% yield (Scheme 75B).



Scheme 75. Synthesis of two CRE cascade reaction precursors containing three internal nucleophiles.

Substrates designed to test the possibility of a CRE cascade reaction with more than three internal nucleophiles were also prepared. Pentaamine **2.167** was synthesised according to a literature procedure[93] (Scheme 76), starting with a conjugate addition reaction of triamine **2.156** with methyl acrylate **2.164**, followed by substitution of the methyl ester **2.165** with methylamine to form amide **2.166**. Reduction of amide **2.166** with lithium aluminium hydride gave pentaamine **2.167** in 60% yield after vacuum distillation.

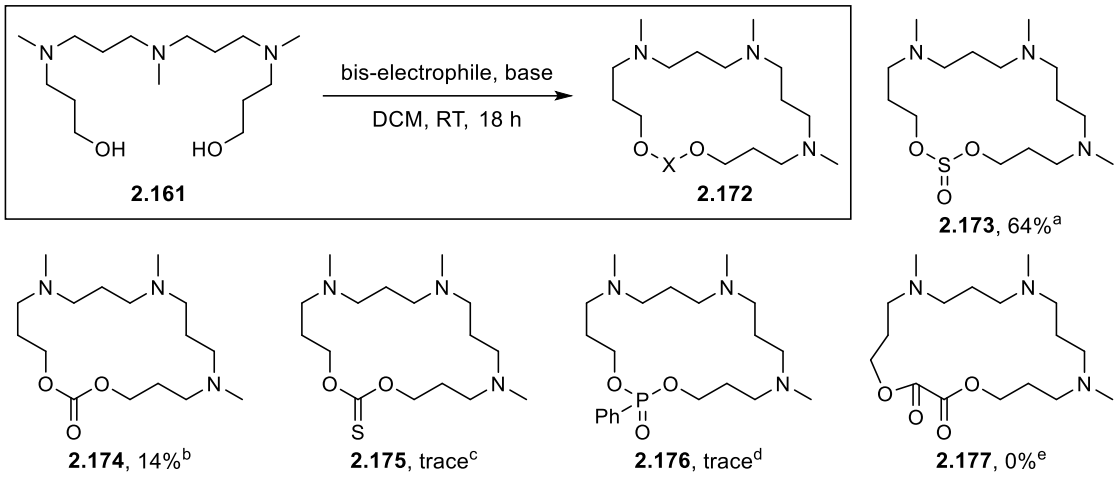
Alkylation of amine **2.167** was first attempted with 3-bromo-propan-1-ol **2.168** however, diol **2.170** could not be isolated by column chromatography as the product was too polar. To get around the polarity issue the alkylation was attempted with bromide **2.169**, which contains a benzyl protected alcohol. It was thought that the benzyl ether **2.171** would be less polar and could therefore be purified by column chromatography, and that following purification the benzyl groups could be removed by hydrogenation, a reaction that typically proceeds cleanly without the need for purification by column chromatography. Disappointingly, the benzyl ether **2.171** was still too polar to be isolated by column chromatography and so no further attempts at synthesising diol **2.170** were carried out. This highlights one of the main challenges of synthesising larger macrocycles using this CRE cascade method. Typically, long synthetic routes are required to reach the desired precursors, and often these precursors are very polar and challenging to purify due to the presence of multiple amine groups that are required for a successful CRE cascade reaction.



Scheme 76. Attempted synthesis of a CRE cascade reaction precursor containing five internal nucleophiles.

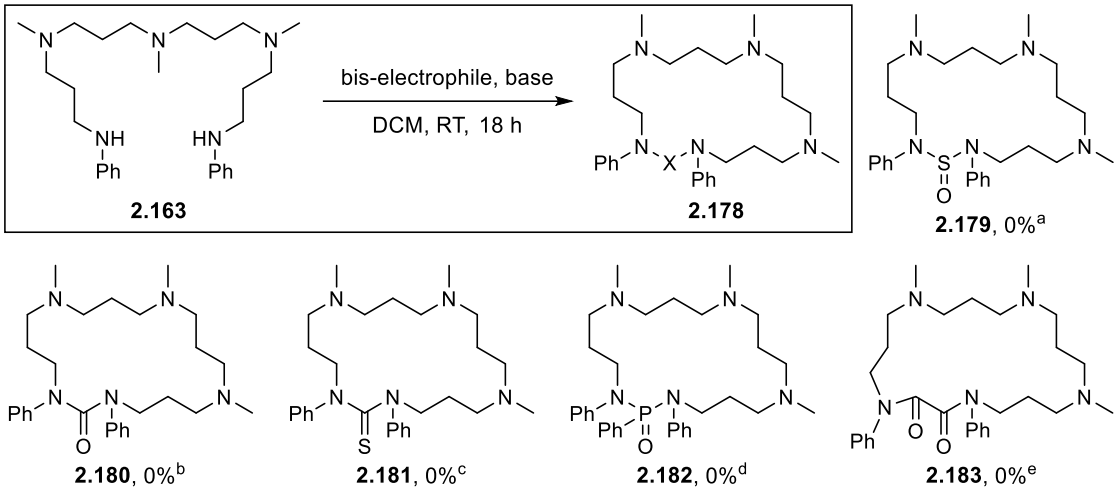
2.8 Cyclisation/Ring Expansion Cascade Reaction with Multiple Internal Nucleophiles Using Bis-Electrophilic Reagents

The CRE cascade reaction of diol **2.161** was attempted using five different electrophiles to give the products shown in Scheme 77. The reaction with thionyl chloride proceeded efficiently and gave the desired 18-membered macrocycle **2.173** in 64% yield. Using triphosgene also worked, giving cyclic carbonate **2.174** albeit in low yield of only 14%. Traces of thionocarbonate **2.175** and phosphonate **2.176** were observed by mass spectrometry although purification of these products was unsuccessful. The reaction with oxalyl chloride showed no evidence for the formation of oxalate **2.177** by ^{1}H NMR spectroscopy or mass spectrometry.



Scheme 77. CRE cascade reactions using a precursor containing three internal nucleophiles. Electrophile/base: [a] $SOCl_2$, DMAP. [b] triphosgene, Et_3N. [c] $CSCl_2$, DMAP. [d] $OPPhCl_2$, DMAP. [e] $(COCl)_2$, Et_3N.

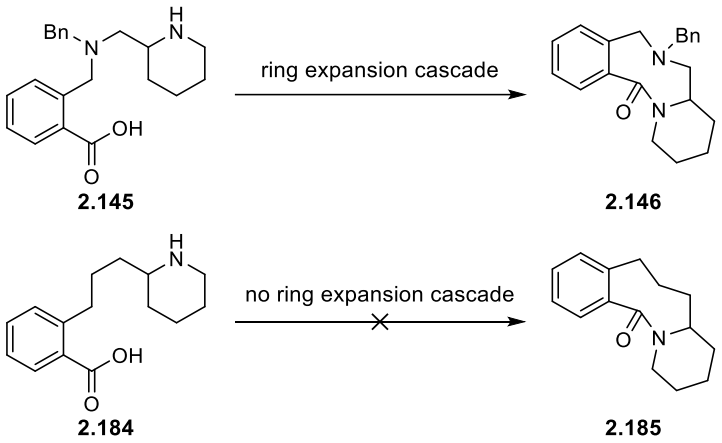
The CRE cascade reaction was attempted on bis-aniline substrate **2.163** (Scheme 78). In all cases, consumption of the starting material **2.163** was observed, however no evidence of any of the desired products **2.179**–**2.183** was observed by mass spectrometry. From the ^1H NMR spectra of the crude reaction mixtures it was clear that a large range of side products were generated which could not be identified. This could be due to the increased reactivity of an aniline, compared to an alcohol, which causes unwanted side reactions to take place.



Scheme 78. Attempted CRE cascade reactions using a precursor containing three internal nucleophiles. Electrophile/base: [a] $SOCl_2$, DMAP. [b] triphosgene, Et_3N. [c] $CSCl_2$, DMAP. [d] $OPPhCl_2$, DMAP. [e] $(COCl)_2$, Et_3N.

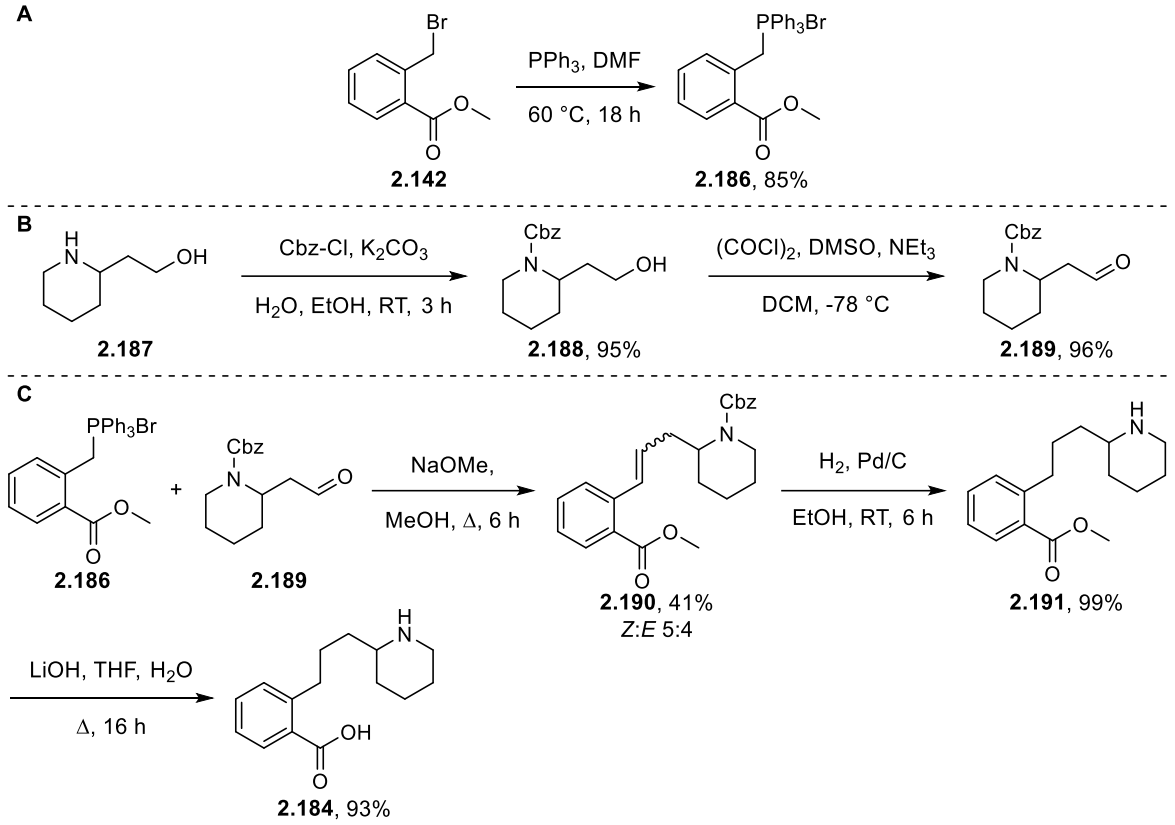
2.9 Control Reaction for a Cyclisation/Ring Expansion Cascade Reaction Using a Single Internal Nucleophile

As mentioned previously, control reactions are often performed where the internal nucleophile is no longer present to test the importance of this internal nucleophile. The CRE cascade reaction to form 8-membered lactam **2.146** proceeded in good yield (82%) and seemed like a good example to demonstrate the importance of the internal nucleophile in this reaction (Scheme 79). In this example, a new precursor **2.184** would need to be synthesised where the tertiary amine of **2.145** is replaced by a CH_2 group which should dramatically decrease the yield of macrocyclisation if the internal nucleophile is catalysing this reaction.



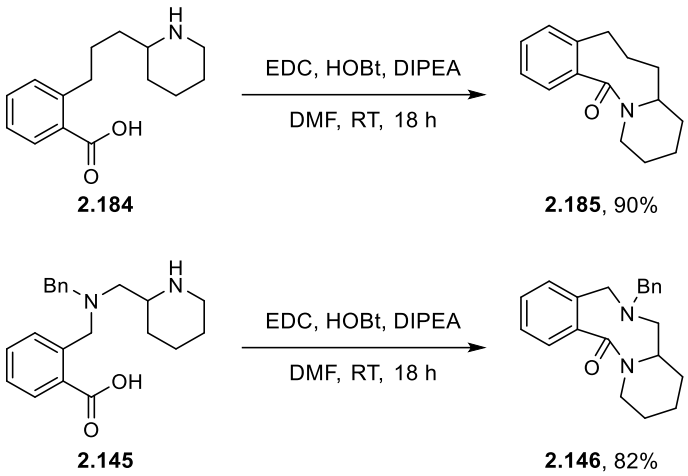
Scheme 79. Proposed control reaction to highlight the importance of the internal nucleophile.

The synthesis of precursor **2.184** was designed around a Wittig reaction to link the phenylene and piperidine fragments of the molecule. The first reagent for the Wittig reaction was synthesised by reacting benzyl bromide **2.142** with triphenylphosphine to give phosphonium bromide **2.186**, in 85% yield (Scheme 80A). The next reagent was synthesised by first *N*-protecting piperidine **2.187** with a Cbz group, which proceeded in 95% yield, followed by a Swern oxidation to yield aldehyde **2.189** in 96% yield (Scheme 80B). With both reagents synthesised, the Wittig reaction was attempted using sodium methoxide to generate the phosphonium ylide *in situ* and this gave the desired alkene **2.190** as a 5:4 mixture of *Z*:*E* isomers in 41% yield (Scheme 80C). The next step was hydrogenation which both reduced the alkene and removed the Cbz to give secondary amine **2.191** in 99% yield. Finally, the methyl ester was hydrolysed using lithium hydroxide to reveal carboxylic acid **2.184** in 93% yield.



Scheme 80. [A] Synthesis of a phosphonium bromide for use in a Wittig reaction. [B] Synthesis of an aldehyde for use in a Wittig reaction. [C] Final steps in the synthesis of the control reaction precursor.

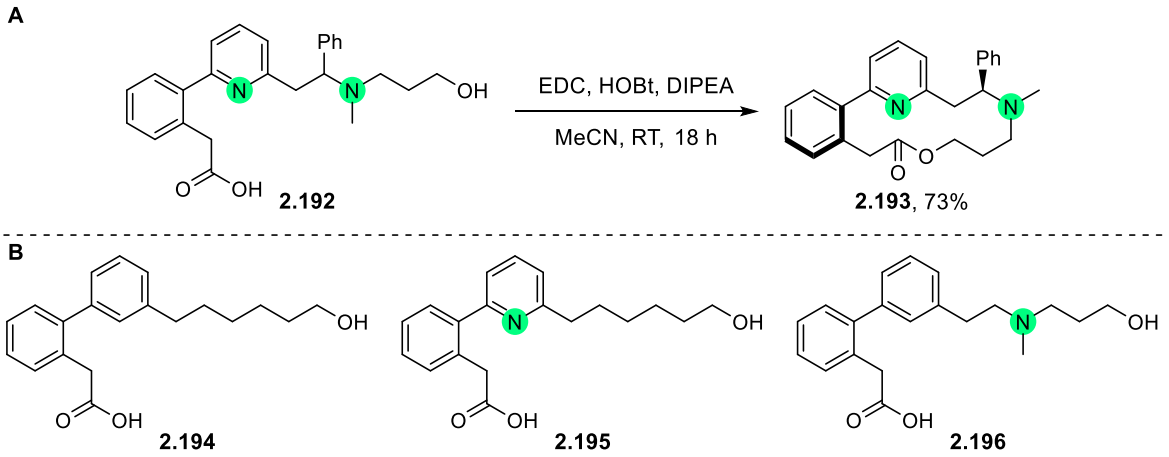
The control reaction was then attempted using EDC/HOBt under the same conditions as the CRE cascade reaction and surprisingly, this gave the 8-membered lactam **2.185** in 90% yield (Scheme 81). This was higher yielding than the analogous CRE cascade reaction which gave lactam **2.146** in 82% yield, suggesting that in this example (**2.145** → **2.146**) direct end-to-end cyclisation is efficient and is therefore likely a competing reaction (or the major pathway) in the formation of **2.146**. This raises an interesting point that, while direct end-to-end cyclisations to form medium-sized rings/macrocycles are typically inefficient and low yielding, there will always be exceptions where cyclisation proceeds efficiently. Example **2.185** is one such exception where direct cyclisation is evidently favourable; this is likely due to amino acid **2.184** being able to access a low energy, reactive conformation that favours cyclisation. It should be noted that within the Unsworth group many more control reactions for the CRE cascade reactions that have been performed that show significantly reduced/no cyclisation when the internal nucleophile is replaced by a non-nucleophilic group.[75,94] Indeed, this is the only instance of the control reaction resulting in a higher yielding than the CRE cascade substrate.



Scheme 81. Control reaction and analogous CRE cascade reaction.

2.10 Control Reactions for a Cyclisation/Ring Expansion Cascade Reaction Using Two Internal Nucleophiles

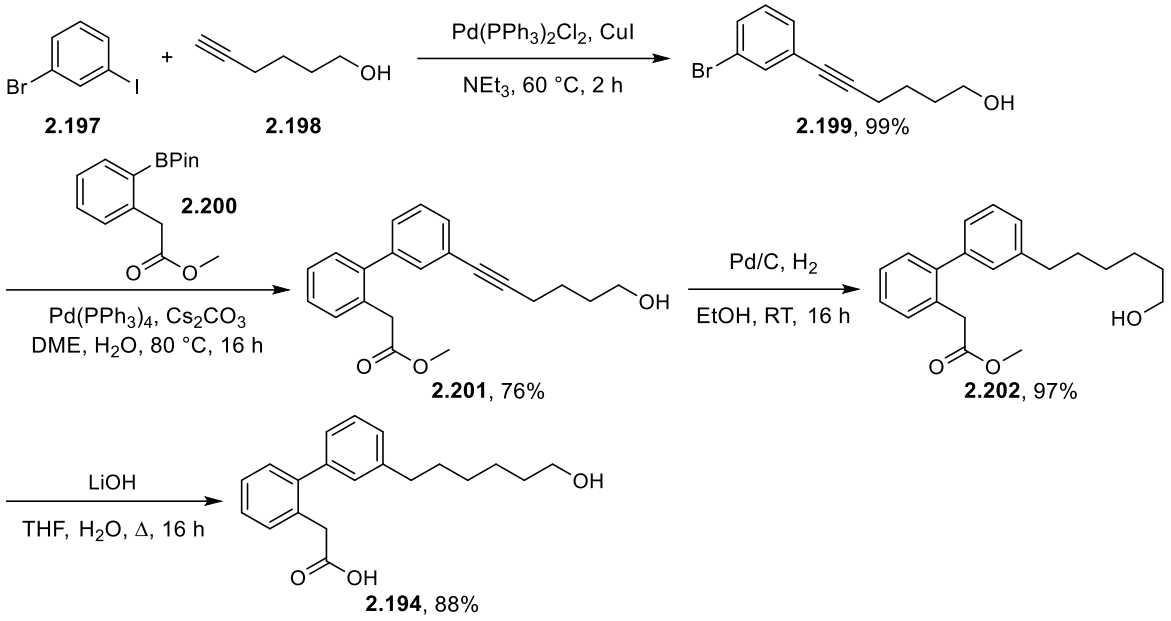
Whilst several control reactions had been performed on single internal nucleophile substrates prior to this PhD project, no control reactions had been performed on a substrate containing two internal nucleophiles. Therefore, it was decided to do this for the CRE cascade reaction outlined in Scheme 82A. In this case, three control reactions can be envisaged, one containing neither internal nucleophile (**2.194**), one containing the first internal nucleophile (**2.195**) and one containing the second internal nucleophile (**2.196**).



Scheme 82. [A] Double internal nucleophile CRE cascade reaction previously done by the Unsworth group. [B] Required precursors for the control reactions.

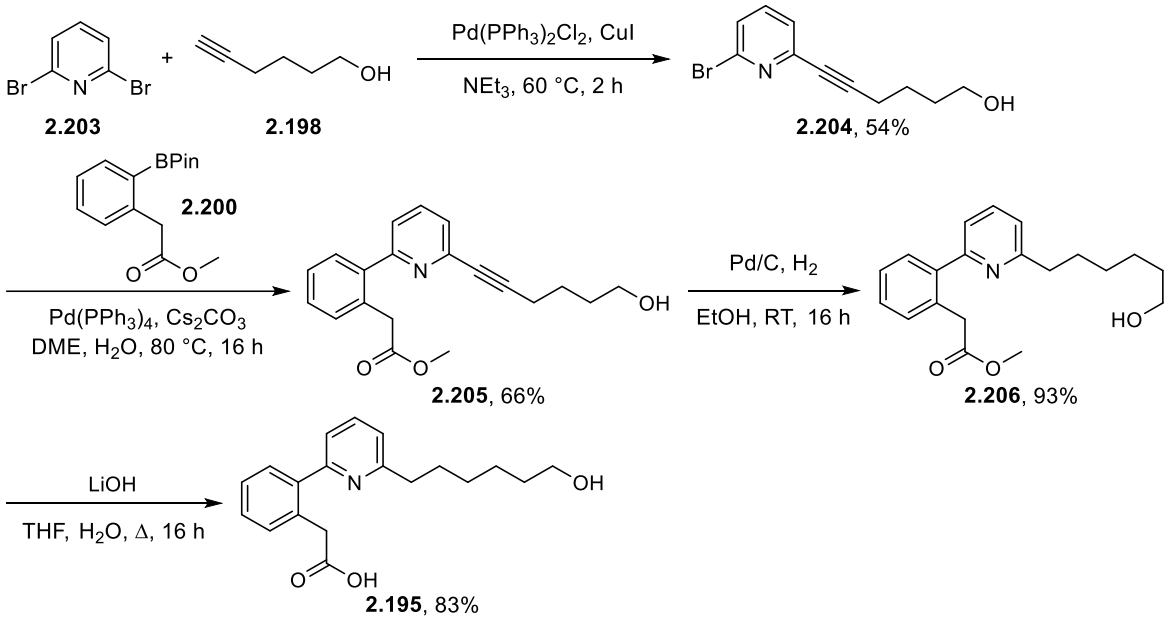
The synthesis of precursor **2.194** started with the Sonogashira coupling of 3-bromoiodobenzene **2.197** and 5-hexyn-1-ol **2.198** which coupled selectively at the iodide position to give alkyne **2.199** in 99% yield (Scheme 83). Hydrogenation of alkyne **2.199** was

attempted but led to dehalogenation and therefore the Suzuki-Miyaura cross-coupling was performed first, using pinacol ester **2.200**, to give the cross-coupled product **2.201** in 76% yield. Alkyne **2.201** was then hydrogenated followed by ester hydrolysis to give the desired carboxylic acid **2.194** in 88% yield.



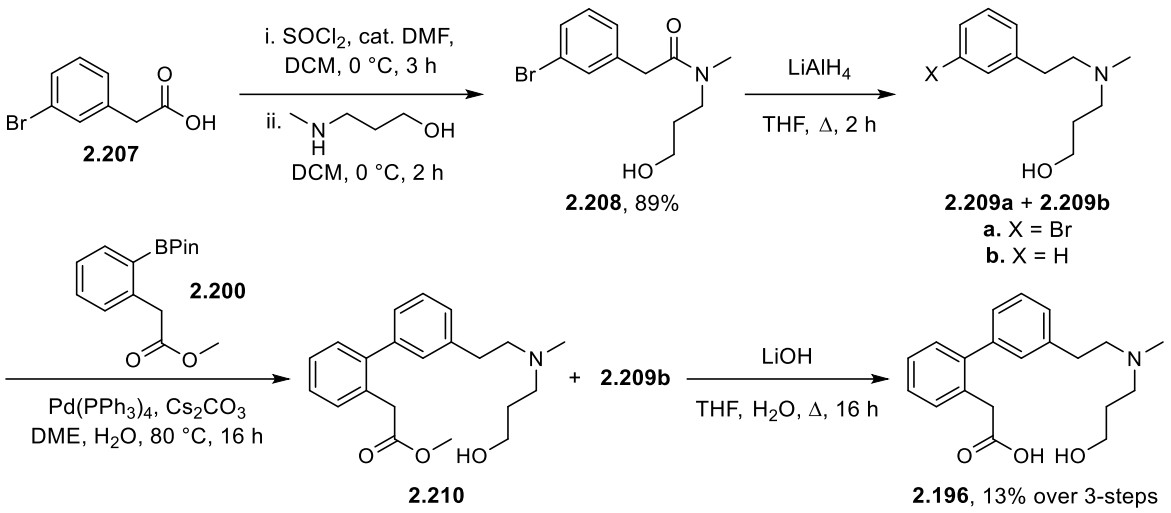
Scheme 83. Synthesis of the control reaction precursor containing none of the internal nucleophiles.

The synthesis of the next precursor (Scheme 84), containing the first pyridyl internal nucleophile, followed the same route as the previous substrate. First, a Sonogashira coupling between 2,6-dibrompyridine **2.203** and 5-hexyn-1-ol **2.198** gave the mono-coupled product **2.204** in 54% yield. This was then cross coupled with pinacol ester **2.200** giving the desired biaryl **2.205** in 66% yield. Hydrogenation reduced the alkyne and subsequent ester hydrolysis gave the carboxylic acid **2.195** in 83% yield.



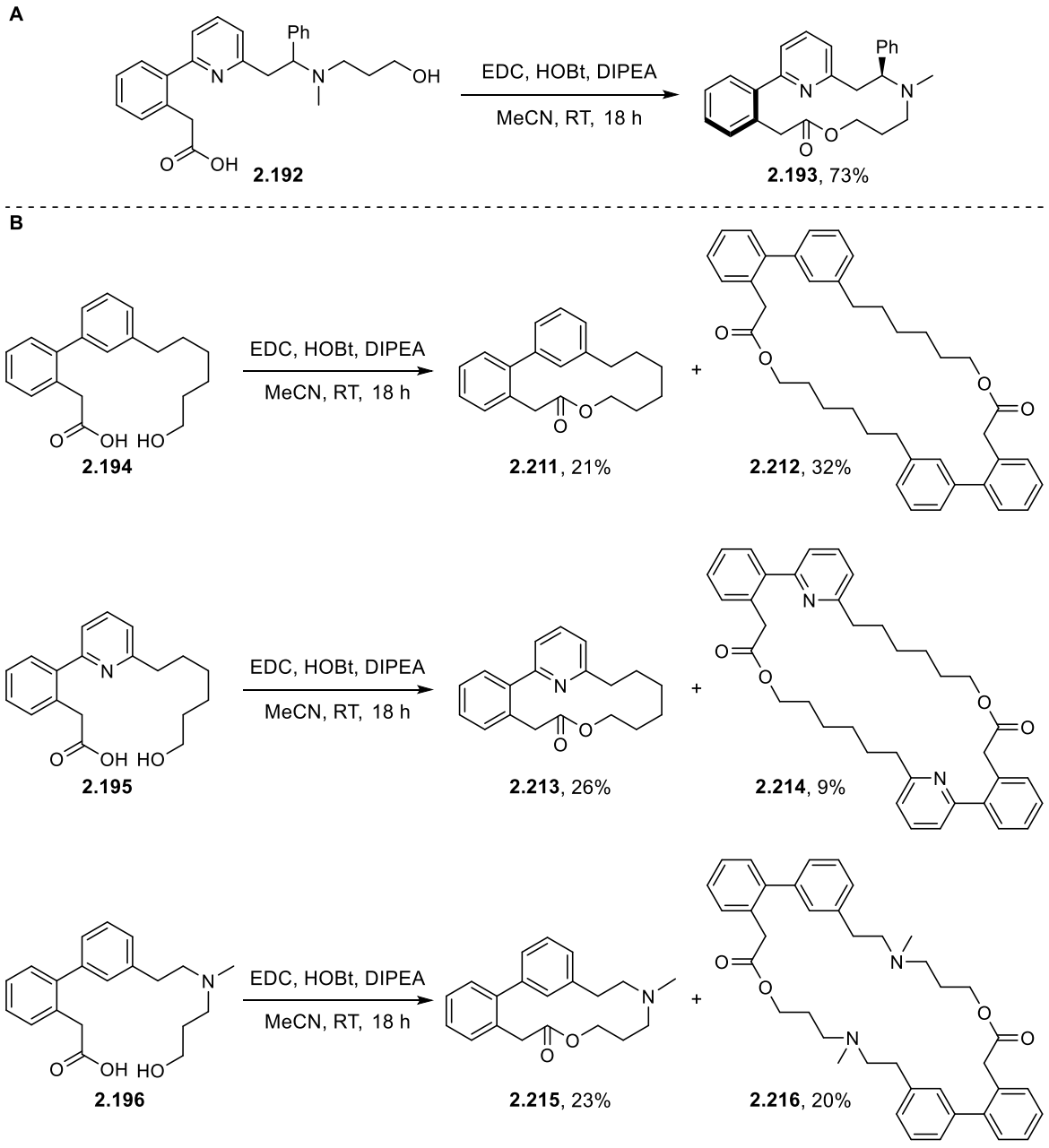
Scheme 84. Synthesis of the control reaction precursor containing the pyridyl internal nucleophile.

The final precursor required a different synthetic route (Scheme 85), this started by converting carboxylic acid **2.207** to an acyl chloride and then reacting this with 3-methylamino-1-propanol to give amide **2.208** in 89% yield over both steps. This was then reduced using lithium aluminium hydride to the desired amine **2.209a**, however, dehalogenated product **2.209b** was also formed and was inseparable from the desired product. This side product should not interfere with the Suzuki-Miyaura reaction and therefore this was carried out on the mixture of products which yielded the biaryl **2.210** although this was again inseparable from side product **2.209b**. The ester hydrolysis was therefore carried out and carboxylic acid **2.196** was isolated as a pure compound in 13% yield over 3-steps.



Scheme 85. Synthesis of the control reaction precursor containing the tertiary amine internal nucleophile.

With the three starting materials successfully synthesised, the control reactions were performed under identical conditions to the CRE cascade reaction to form **2.193**, which proceeds in 73% yield. (Scheme 86A). In each case the cyclised products **2.211** (no internal nucleophiles), **2.213** (first internal nucleophile) and **2.215** (second internal nucleophile) were obtained in just 21%, 26% and 23% respectively (Scheme 86B). These results clearly highlight the importance of both internal nucleophiles being present, with the yield decreasing by ca. 50% when one or both internal nucleophiles are not included. In each case the head-to-tail dimers **2.212**, **2.214**, and **2.216** were also isolated in 32%, 9% and 20% yield respectively, clearly indicative of competing intermolecular reactions. In the case of dimer **2.214**, an X-ray crystal structure was obtained confirming this was a dimer (Figure 5). The remaining starting material likely comprises polymerised side products that could not be isolated by column chromatography.



Scheme 86. [A] Double internal nucleophile CRE cascade reaction previously done by the Unsworth group. [B] Control reactions highlighting the importance of both internal nucleophiles.

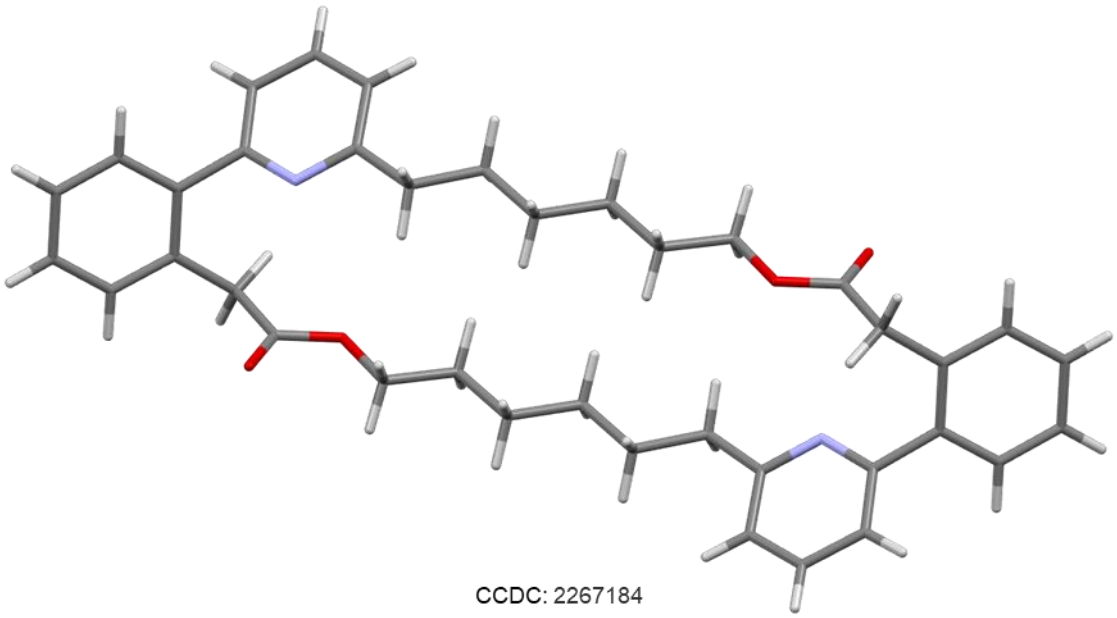


Figure 5. X-ray crystal structure of head-to-tail dimer **2.214**.

2.11 Conclusion

In conclusion the scope of the CRE cascade reaction was expanded by using biaryl precursors with bis-electrophilic reagents. This allowed medium-sized rings bearing carbamate, sulfite ester and sulfuramidite functional groups to be synthesised *via* CRE cascade reactions. One example of CRE cascade reaction using a biaryl precursor was also shown to proceed diastereoselectively, although this product was found to be prone to decomposition.

The exploration of imines as internal nucleophiles showed that imines are not compatible with the CRE cascade reaction. Attempts with imine-based precursors typically led to cyclisation at the imine position leading to tricyclic side products forming. Attempts to suppress this side reaction, involving removing the base and designing to substrates with sterically bulky groups adjacent to the imine, were unsuccessful. This was thought to be due to an equilibrium between the desired medium-sized ring and the tricyclic side product which DFT calculation suggested lies entirely towards the side product. Due to this it is unlikely that imines will be feasible internal nucleophiles in the CRE cascade reaction.

The CRE cascade reaction of substrates bearing multiple internal nucleophiles was found to be successful. A CRE cascade reaction based on two internal amine nucleophiles was successful giving a 12-membered macrocycle in 59% yield. The CRE cascade reaction with a substrate containing three internal nucleophiles was also successful with an 18-

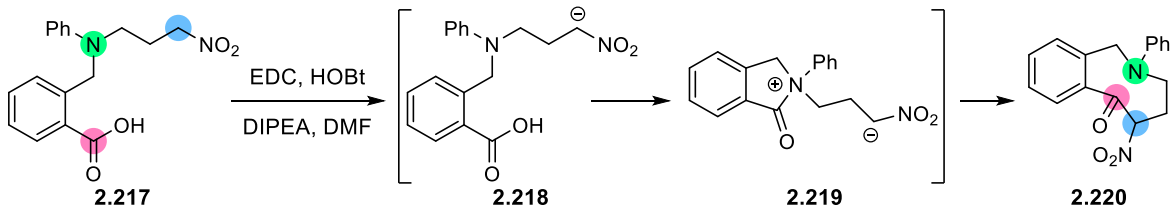
membered macrocycle being synthesised in 64% yield showing that longer cascade processes are feasible. The main challenge with these longer cascade reactions is the synthesised of the precursors, with several attempts at synthesising these being unsuccessful, typically due to the highly polar nature of the desired products.

Finally, control reactions for a CRE cascade reaction with two internal nucleophiles were carried out. The results of these clearly highlight the importance of both internal nucleophiles, as when one or both are not included, the yield of the reaction significantly decreased by ca. 50%. Along with the other control reaction done by the Unsworth group,[75,94] there is strong evidence supporting the operation of the proposed internal nucleophile catalysed pathway.

The results described in this Chapter are published in the *Journal of the American Chemical Society*.[94]

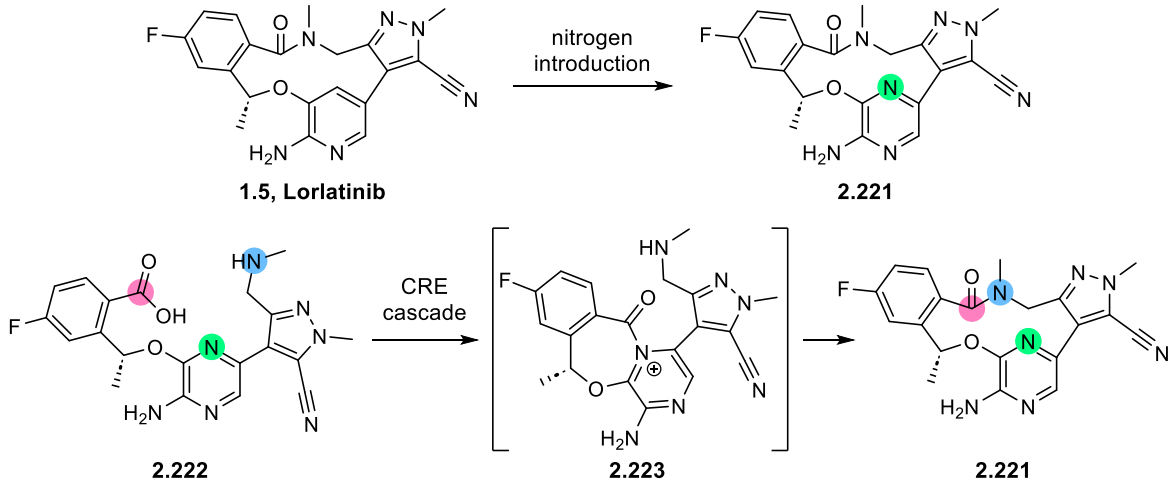
2.12 Future Work

One possibility for future work is the exploration of carbon-centred nucleophiles (Scheme 87), as no attempt at using these in the CRE cascade reaction has been made. A good starting point for this would be using a nitro- group which likely has a similar pK_a to DIPEA (ca. 10) which is used in the standard CRE cascade reaction conditions. This means that under the reaction conditions, substrate **2.217** could be deprotonated to give anion **2.218**. Initial cyclisation of the aniline internal nucleophile gives intermediate **2.219** which can then undergo cyclisation and fragmentation using the carbanion to give α-nitro ketone **2.220**. This α-nitro ketone group could then undergo more diverse functionalisation reactions for example, ketone reduction to the alcohol or reduction of the nitro group to an amine which could then be reacted further, allowing a more diverse array of structures to be generated.



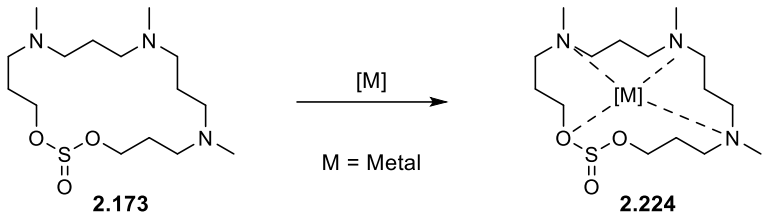
Scheme 87. Potential CRE cascade reaction using a carbon-centred terminal nucleophile.

It would also be interesting to explore the possibility of synthesising drug-like molecules using the CRE cascade reaction. Although it is unlikely that any current drug on the market can be synthesised using this ring expansion approach, many can be modified by the introduction of heteroatoms that would allow a CRE cascade reaction to take place (Scheme 88). One such example of this is the drug Lorlatinib **1.5**, which is synthesised *via* a direct end-to-end cyclisation using an amide coupling reaction.[95] Introducing a nitrogen atom into the pyridine ring gives pyrazine analogue **2.221** which could be synthesised *via* a CRE cascade reaction. The starting material for this reaction would be carboxylic acid **2.222** which could undergo a cyclisation to give 7-membered intermediate **2.223**, followed by a second cyclisation and fragmentation to give Lorlatinib analogue **2.221**. This approach would hopefully negate the need for the slow addition of reagents, that was carried out over 16 hours, in the synthesis Lorlatinib **1.5**.



Scheme 88. Introduction of a nitrogen atom into the drug Lorlatinib that would allow a CRE cascade reaction to take place.

Finally, it would be interesting to explore the potential applications of the medium-sized rings and macrocycles synthesised by the CRE cascade reaction. Due to the presence of multiple heteroatoms in backbone of the synthesised macrocycles, they could be used as chelating ligands for metals (Scheme 89). These macrocycles could therefore prove useful ligands in transition-metal catalysed reactions, as cation binders to increase the reactivity of an anion in solution, or potentially as chelating ligands to aid in precious metal recycling.



Scheme 89. Potential chelation effect of a macrocycle synthesised *via* the CRE cascade approach.

3 Atroposelective Amide Synthesis

3.1 Introduction

Axial chirality arises when a molecule contains an axis about which a set of substituents are held in a spatial arrangement that is not superimposable on its mirror image. This is most commonly encountered in allenes (Figure 6A),[96] where there is hindered rotation due to the π- bonds, and also in biaryl systems, where there is restricted rotation about the single bond joining the two ring systems (Figure 6B). In the latter case, the isomers are known as atropisomers; by definition, atropisomers are conformers that interconvert with a half-life of >1000 seconds at a given temperature.[97] As atropisomers are conformers, racemisation can occur *via* bond rotation and the rate of this is determined primarily by the steric bulk of the *ortho*- substituents, meaning that the half-life of a pure enantiomer can range from seconds to thousands of years depending on the substitution pattern of the rings.

Historically, studies on the synthesis and properties of atropisomers has focused on biaryl compounds, compounds which find a wide variety of uses, as was discussed in Chapter 1. A small selection of chiral biaryl molecules are shown in Figure 6C, with applications in chiral catalysis,[76–78] supramolecular chemistry[1] and pharmaceuticals.[82–84]

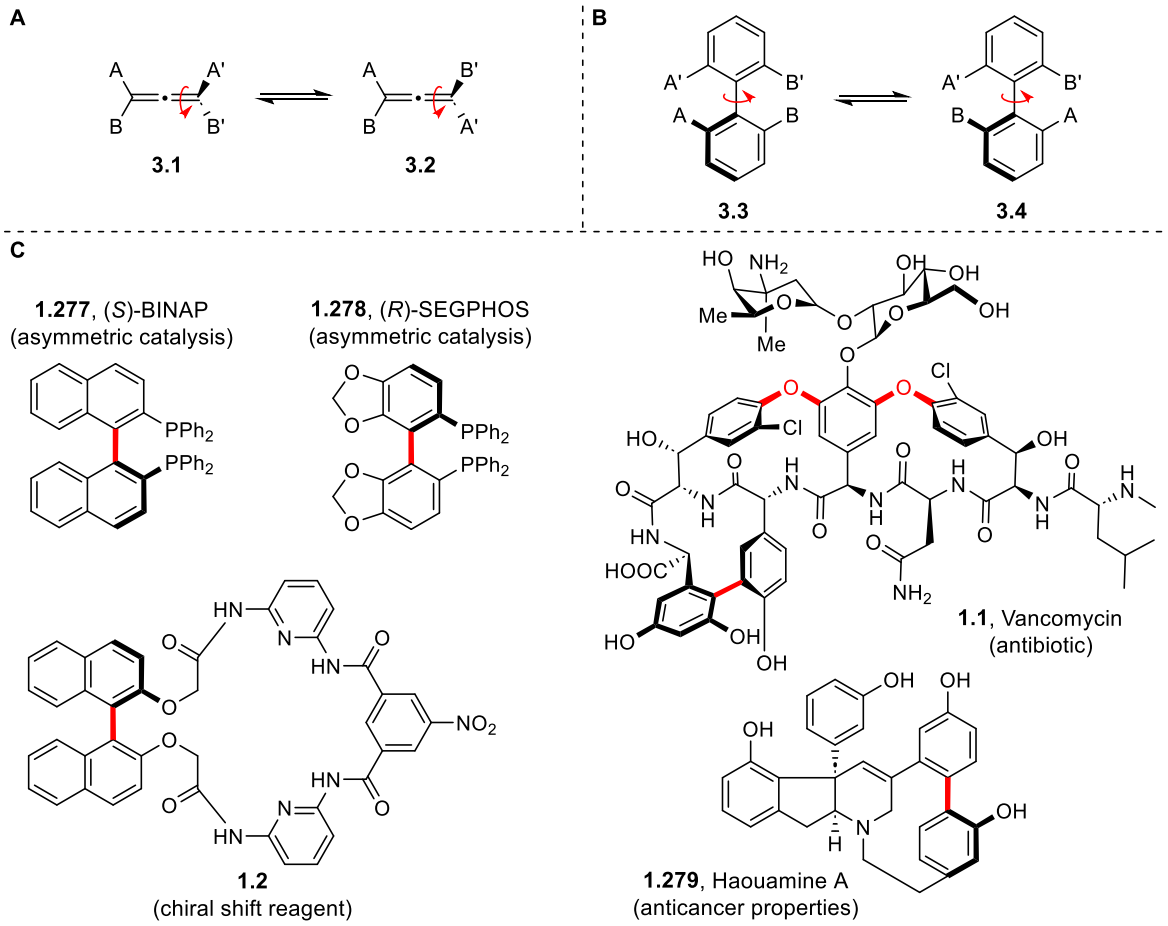


Figure 6. [A] Axial chirality in allenes where there is restricted rotation due to the π-orbitals of the double bonds. [B] Axial chirality in biaryls where there is restricted rotation about the single bond joining the two rings due to steric factors. [C] Examples of chiral biaryl molecules.

Atropisomerism is not limited to biaryl compounds, other classes of molecules that show this property are diaryl ethers/diarylamines,[98] benzamides,[99] sulfonamides/phoshponamides and anilides[100] (Figure 7). This work will focus on anilides which, although they have received much less attention than biaryl atropisomers, still find important uses and have received much interest in recent years. One such example is metolachlor, a herbicide that has been widely used since the 1970s. Anilides are also pharmaceutically relevant, methaqualone was used as a sedative in the mid–late 1900s and in 2021 the FDA approved a new drug sotorasib as an anti-cancer treatment which targets mutant KRAS proteins, and is the first drug to achieve this.

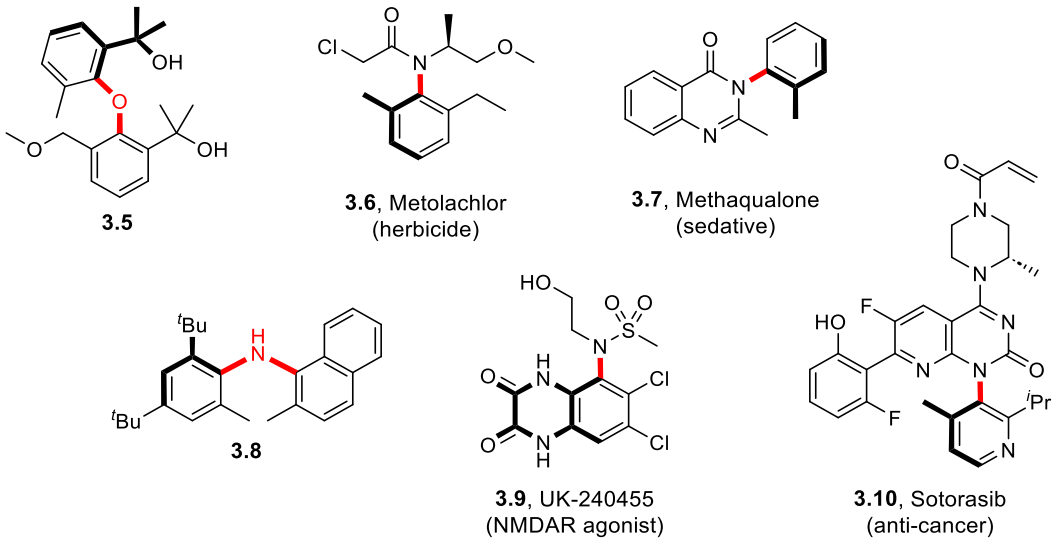
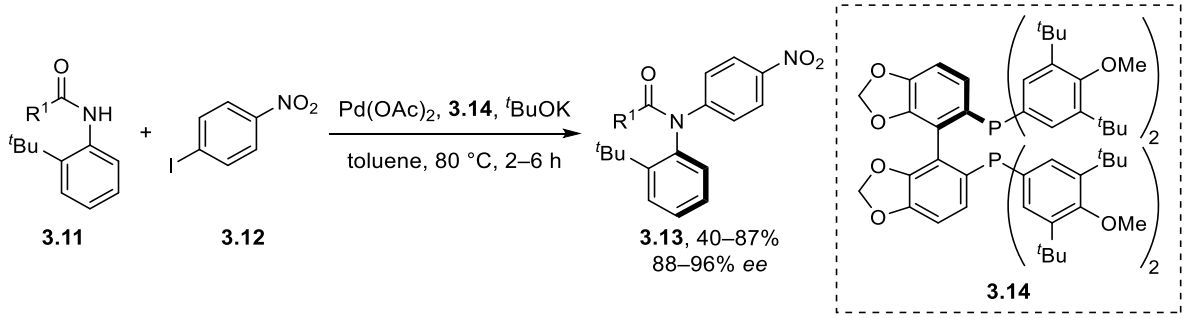


Figure 7. Examples of non-biaryl atropisomers with the chiral axes highlighted in red.

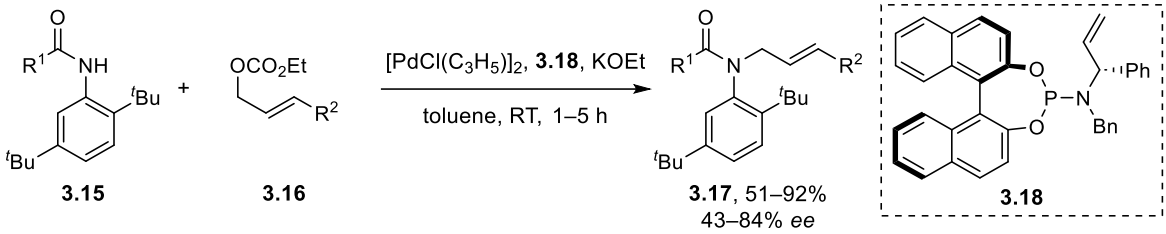
Despite the recent interest in atropisomeric anilides, their stereoselective synthesis remains a challenge, with a limited number of strategies available to chemists.[101,102] Taguchi and co-workers reported an enantioselective Buchwald-Hartwig amination using palladium acetate with chiral phosphine ligand **3.14** (Scheme 90).[103] This method allowed the synthesis of chiral anilides in up to 96% *ee* and showed broad scope with respect to the aniline substrate **3.11**. The scope of the iodide substrate was much more limited and was only successful with nitro- substituted aryl iodides such as **3.12**. It is likely that a more reactive, electron deficient iodide is required to react efficiently with the sterically congested anilide moiety.



Scheme 90. Enantioselective Buchwald-Hartwig amination of *tert*-butyl anilides.

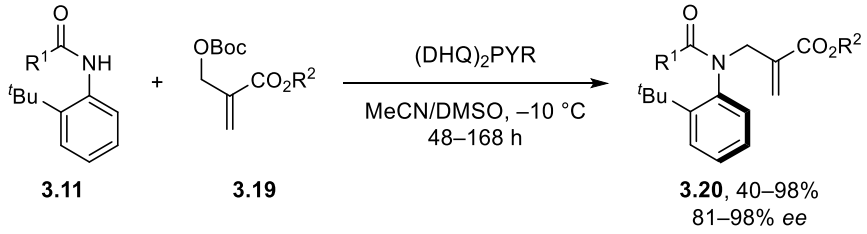
Du and co-workers reported an enantioselective Tsuji-Trost allylation using an allylpalladium chloride catalyst with chiral phosphine ligand **3.18** (Scheme 91).[104] Allylation of anilides **3.15** using carbonates **3.16** proceeded efficiently, typically giving the products in high yield with up to 84% *ee*. A broad substrate scope was carried out on both the anilide **3.15** and carbonate **3.16** fragments and the reaction was found to be tolerant of a range of

functional groups. Alternatives to the *o-tert*-butyl substituents were also used, such as di-*ortho*- substituted anilines, although the *ee* of these reactions were significantly lower (up to 53% *ee*) than the *tert*-butyl analogues.



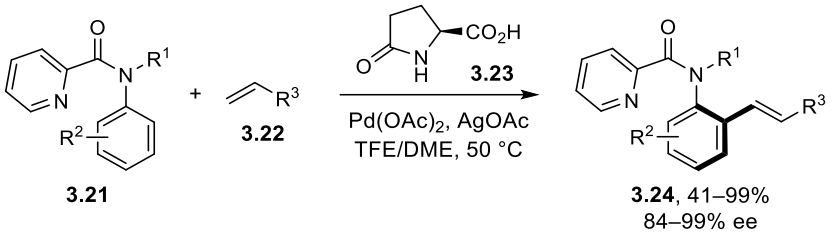
Scheme 91. Enantioselective Tsuji-Trost allylation of *tert*-butyl anilides.

Li and co-workers also reported an asymmetric allylation which does not use a palladium catalyst (Scheme 92).[105] In this work, anilides **3.11** were reacted with Morita-Baylis-Hillman carbonates **3.19** in the presence of bis-Cinchona alkaloid ligand $(DHQ)_2PYR$ which gave the allylated products **3.20** typically in high yields with up to 98% *ee*. It was found that the highest *ee* was obtained by carrying the reaction out at –10 °C, although this led to long reaction times, in some cases up to seven days.



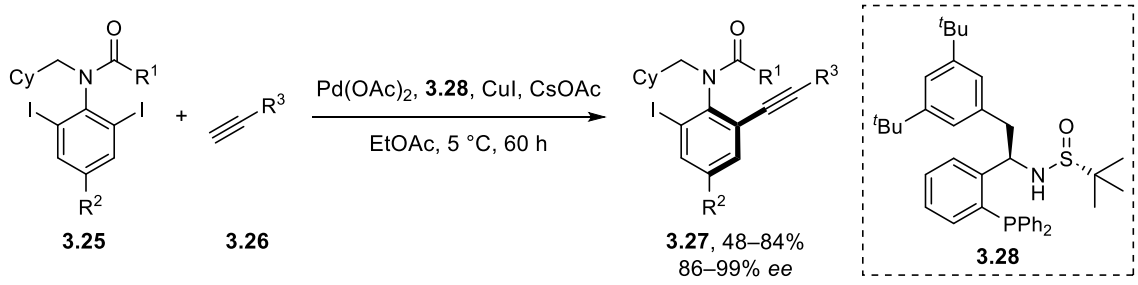
Scheme 92. Enantioselective allylation using Morita-Baylis-Hillman carbonates.

It is also possible to generate chiral anilides *via* functionalisation of the aniline ring system. Shi and co-workers reported a C–H activation strategy, using palladium acetate and pyroglutamic acid ligand **3.23**, to functionalise the *ortho*- position of anilides **3.21** (Scheme 93).[106] This allowed the dynamic kinetic resolution of anilides **3.21** to give the di-*ortho*-substituted anilides **3.24** in up to 99% *ee* and predominantly as the *E*-isomer. For this process to work, C–N rotation needed to occur in the precursors **3.21**, meaning that less bulky *ortho*- substituents typically gave higher yields (*i.e.* R^2 = *o*-^{i}Pr or *o*-Me). When bulkier substituents were used (*i.e.* R^2 = *o*-^{t}Bu), C–N rotation in the starting material was sufficiently hindered which meant a kinetic resolution effect was observed, with the product being isolated in only 37% yield and 94% *ee*.



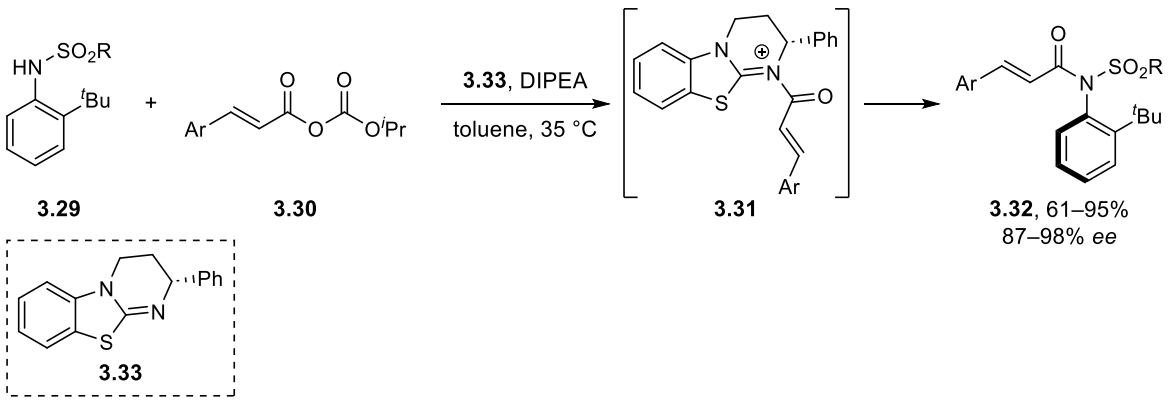
Scheme 93. Dynamic kinetic resolution through a palladium catalysed C–H activation reaction.

Zhang and co-workers performed an enantioselective Sonogashira coupling reaction on diiodo- substituted anilides **3.25** (Scheme 94).[107] Using palladium acetate, copper iodide and chiral phosphine ligand **3.28**, the mono-substituted alkynes **3.27** could be generated in 48–84% yield with only small amounts of the di-substituted being observed. Due to the small steric bulk of the alkyne moiety, the C–N rotational barrier was relatively low, and therefore the reactions were conducted at 5 °C to obtain the optimal *ee* (up to 99%) although this meant long reaction times were required (60 h).



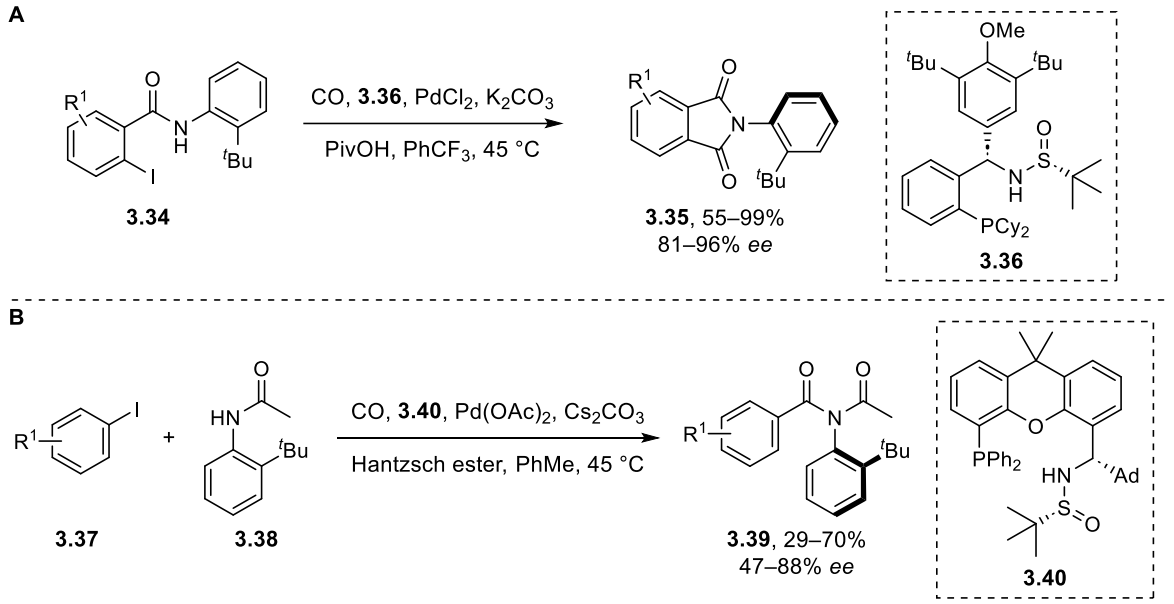
Scheme 94. Synthesis of axially chiral anilides via a palladium/Ming-Phos catalysed Sonogashira reaction.

Asymmetric acylation reactions have also been demonstrated to be a viable method to synthesise chiral anilides. Dong and co-workers reported an enantioselective acyl transfer reaction using a chiral isothiourea catalyst **3.33** (Scheme 95).[108] In this reaction, isothiourea **3.33** reacts with anhydride **3.30** to give chiral acylisothiouronium intermediate **3.31**, which then acylates sulfonamide **3.29** to yield the chiral anilides **3.32** in up to 98% *ee*. A large range of anhydrides were tolerated although these were typically limited to vinylic anhydrides. One example using acetic anhydride was attempted and gave the desired product in 90% *ee* but in a significantly lower yield (44%) than the vinylic anhydrides.



Scheme 95. Enantioselective acylation of sulfonamides.

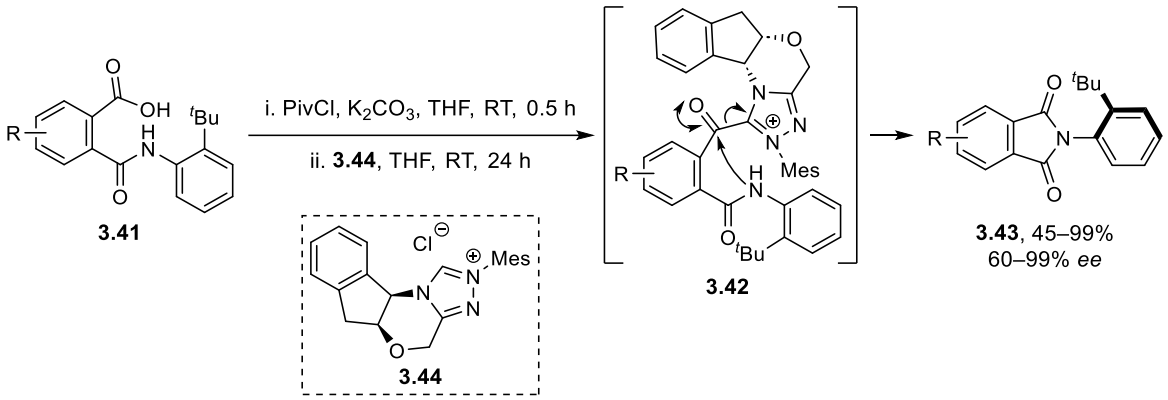
Li and co-workers developed an enantioselective CO insertion process using palladium chloride, carbon monoxide and chiral phosphine ligand **3.36**.[109] Using aryl iodide **3.34** as the substrate allowed for an intramolecular cyclisation process to furnish the phthalimides **3.35** in up to 99% *ee* (Scheme 96A). They also demonstrated the possibility of an intermolecular process by reacting aryl iodides **3.37** with anilides **3.38** to give acyclic imides **3.39** (Scheme 96B). This was more challenging than the intramolecular cyclisations and typically gave lower yields and slightly reduced *ee* (up to 88%).



Scheme 96. [A] Intramolecular enantioselective carbonylation of aryl iodides with anilides. [B] Intermolecular enantioselective carbonylation of aryl iodides with anilides.

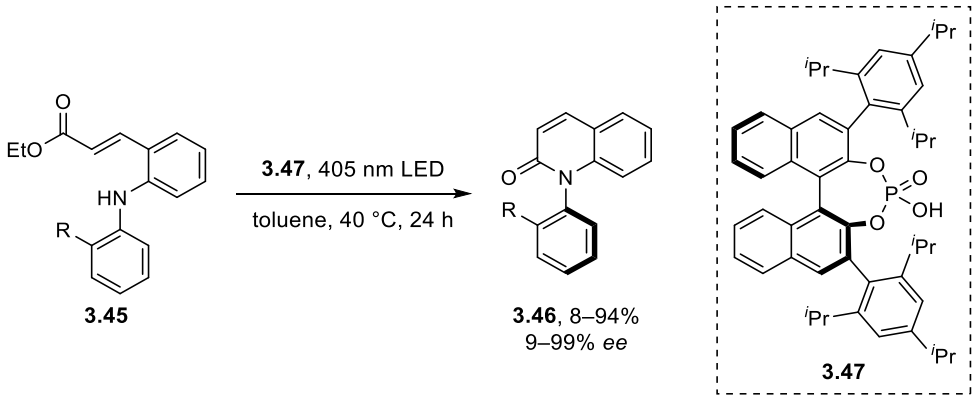
Biju and co-workers also reported an enantioselective synthesis of phthalimides from benzoic acid precursors, that did not require the use of palladium catalysis (Scheme 97).[110] Benzoic acid **3.41** was first activated with pivaloyl chloride, followed by reaction with

a chiral *N*-heterocyclic carbene generated from pre-catalyst **3.44**. This led to the formation of chiral intermediate **3.42** which undergoes intramolecular cyclisation to give the phthalimides **3.43** in up to 99% *ee*. This mild and selective method was tolerant of a wide range of functionalities typically giving the products in near quantitative yield. The authors also demonstrated the utility of these products by performing a range of functionalisation reactions without significant loss of enantiopurity.



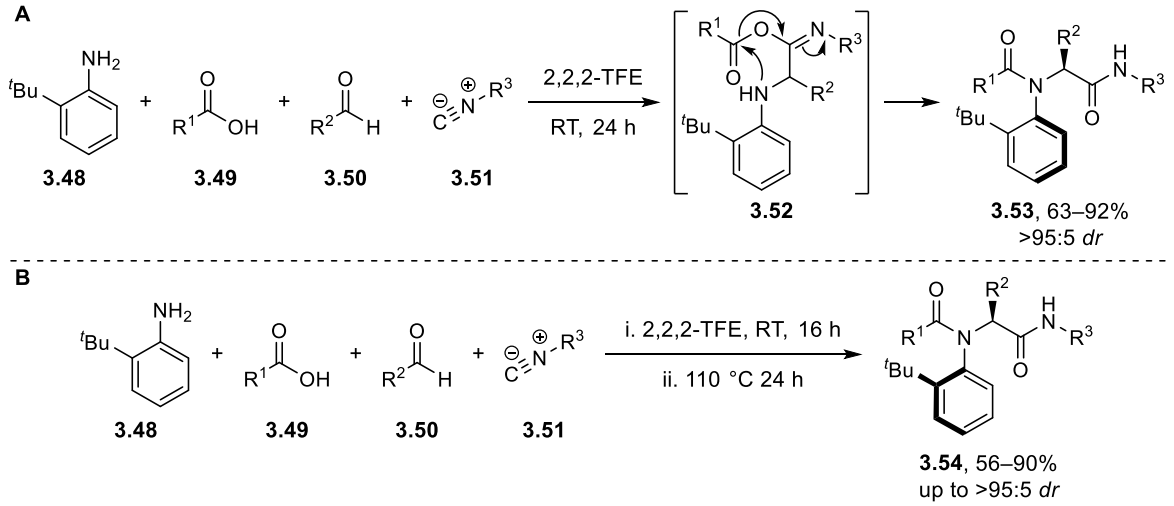
Scheme 97. Enantioselective synthesis of phthalimides using an *N*-heterocyclic carbene catalyst.

Doerfler and co-workers used and acid-catalysed photocyclization to synthesise *N*-aryl quinolones enantioselectivity (Scheme 98).[111] Irradiation of alkene **3.45** with a 405 nm LED induced an isomerisation reaction to the *Z*- isomer, which then underwent a cyclisation reaction catalysed by the chiral phosphate **3.47** to give quinolones **3.46**. Enantiomeric excess up to 99% could be achieved when methoxy substituents were used (R = OMe), although when a different substituent was used (*e.g.* R = alkyl or halide) a significant decrease in *ee* and yield was noted. The reaction also proceeded efficiently with di-substituted anilines, if one of the substituents was an *ortho*-methoxy group, suggesting methoxy groups are important in facilitating the cyclisation process.



Scheme 98. Atroposelective Brønsted acid-catalysed photocyclization.

Armstrong and co-workers recently reported an elegant multi-component Ugi reaction that allowed the diastereoselective synthesis of *tert*-butyl anilides **3.53** (Scheme 99A).[112] This reaction, involving aniline **3.48**, carboxylic acid **3.49**, aldehyde **3.50** and isocyanide **3.51**, leads to the formation of intermediate **3.52** which then undergoes an acyl transfer reaction to give anilides **3.53** as a racemic mixture of one diastereoisomer. This reaction had a very broad scope with all four components being varied to generate 42 examples of anilides in 63–92% yield. It was also demonstrated that by heating the reaction mixture to 110 °C, after the initial reaction, the product could epimerise to give the thermodynamically favourable isomer **3.54** in good yields and *dr* (Scheme 99B). This meant that both diastereoisomers could be synthesised directly.

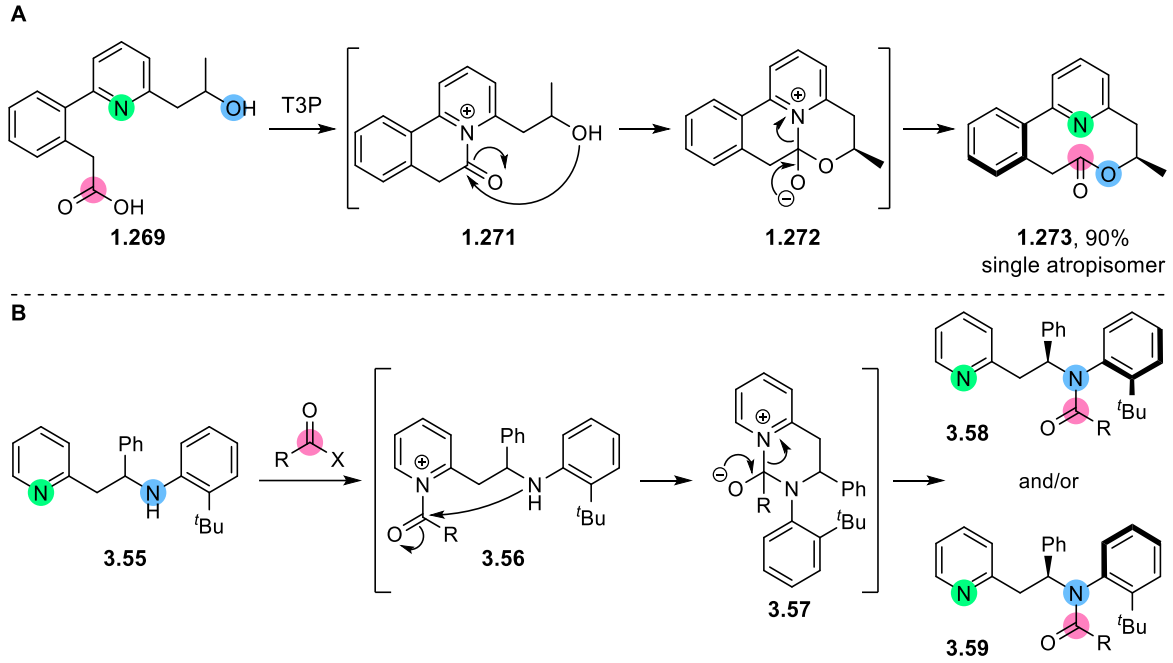


Scheme 99. [A] Diastereoselective multicomponent Ugi reaction for the synthesis of anilides. [B] Stereodivergent reaction allowing access to the alternate diastereoisomer.

3.2 Project Aims

The aim of the work described in this Chapter was to develop a new method for the atroposelective synthesis of anilides, inspired by an atroposelective ring expansion cascade reported by the Unsworth group.[75,94] In this previous work (Scheme 100A) a linear carboxylic acid (*e.g.* **1.269**) was activated with T3P which led to an initial cyclisation to form the acyl pyridinium **1.271**, followed by a second cyclisation to form the bicyclic intermediate **1.272** which fragmented forming the medium-sized ring **1.273** as a single atropisomer. It was envisaged that a similar result could be obtained by reacting *tert*-butylaniline **3.55** with an acylating agent (*e.g.* an activated carboxylic acid or an acyl chloride). In this case it was expected that the pyridine would acylate first (**3.55** → **3.56**) and then an intramolecular

acyl transfer would take place (**3.56** → **3.57** → **3.58**), ideally giving the product as a single atropisomer *i.e.* **3.58** or **3.59** only (Scheme 100B).

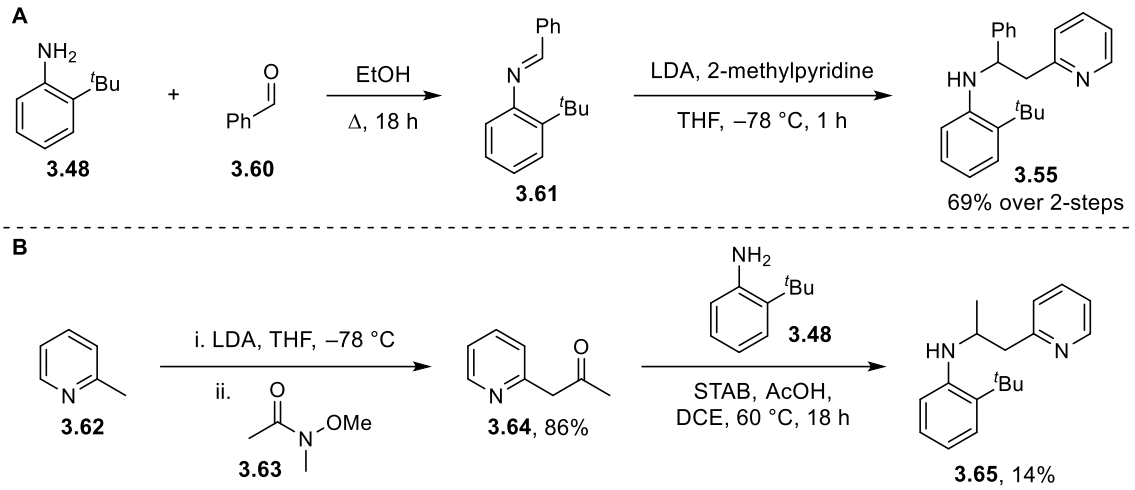


Scheme 100. [A] Previous atroposelective ring expansion reaction. [B] Proposed atroposelective acyl transfer reaction.

3.3 Starting Material Synthesis

Various precursors for the acyl transfer reaction were synthesised to explore the scope of this reaction, typically using short, high-yielding syntheses. The first of these (Scheme 101A) was synthesised by first reacting *tert*-butylaniline **3.48** with benzaldehyde **3.60** to give imine **3.61**. 2-Methylpyridine could then be deprotonated with LDA, forming an organolithium species which was trapped with imine **3.61** to give amine **3.55**, the desired precursor, in 69% yield over both steps.

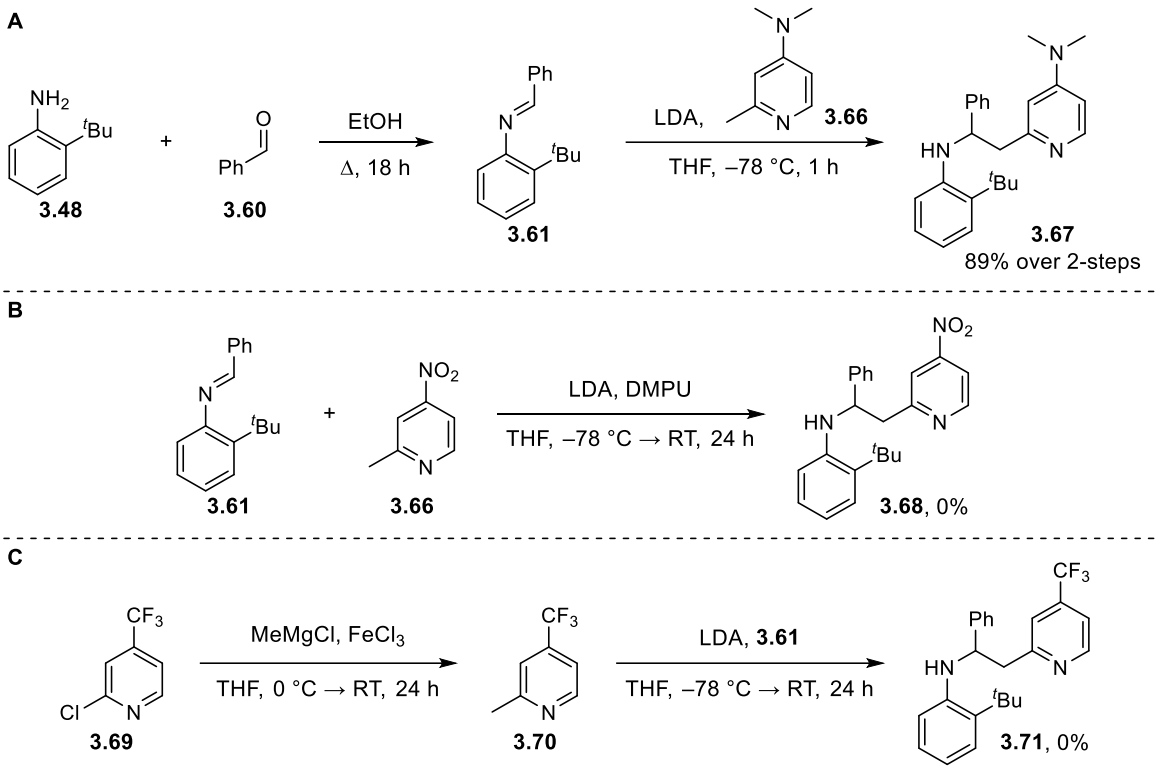
A second precursor was synthesised in which the phenyl substituent was replaced by a smaller methyl substituent (Scheme 101B). First, 2-methylpyridine **3.62** was deprotonated with LDA and then reacted with Weinreb amide **3.63** to give the monoacylated product **3.64** in 86% yield. Reductive amination with *tert*-butylaniline **3.48** then gave the desired precursor **3.65**. Although the yield for this reaction was low (14%), and could likely be improved, no optimisation was performed as enough material was acquired to carry out the acyl transfer reaction.



Scheme 101. Synthesis of starting materials that proceed *via* a 6-memebered cyclic transition state.

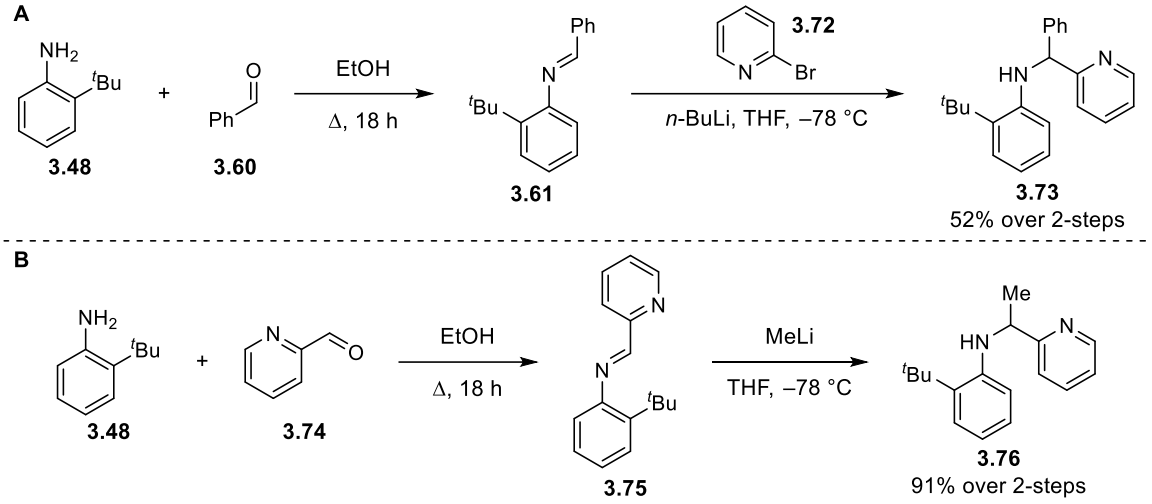
A substituted pyridyl precursor was also synthesised using the same lithiation strategy (Scheme 102A). Methylpyridine **3.66** was lithiated with LDA and then trapped with imine **3.61** to form the electron rich pyridyl precursor **3.67**, which is analogous to the commonly used pyridine-base catalyst DMAP. The synthesis of an electron deficient pyridyl precursor was attempted using methylpyridine **3.66**, with DMPU used to increase the solubility of the lithiated species (Scheme 102B). This was unsuccessful with no evidence of the desired amine product **3.68** and both starting materials **3.61** and **3.66** being observed by ^{1}H NMR after work-up. This could be due to the electron withdrawing effect of the nitro group stabilising the lithiated intermediate and thus making it less reactive.

The synthesis of a precursor bearing a trifluoromethyl group was also attempted with the hope that the weaker electron withdrawing effect would allow the lithiation trapping to proceed more efficiently (Scheme 102C). Chloropyridine **3.69** was reacted with methylmagnesium chloride to give methylpyridine **3.70**, which was then used in the lithiation reaction. Unfortunately, no evidence of the desired product **3.71** was observed by ^{1}H NMR and the imine remained unchanged during the course of the reaction. This is likely due to the same reason as the nitro example and therefore no further attempts were made to synthesise a precursor with an electron withdrawing group.



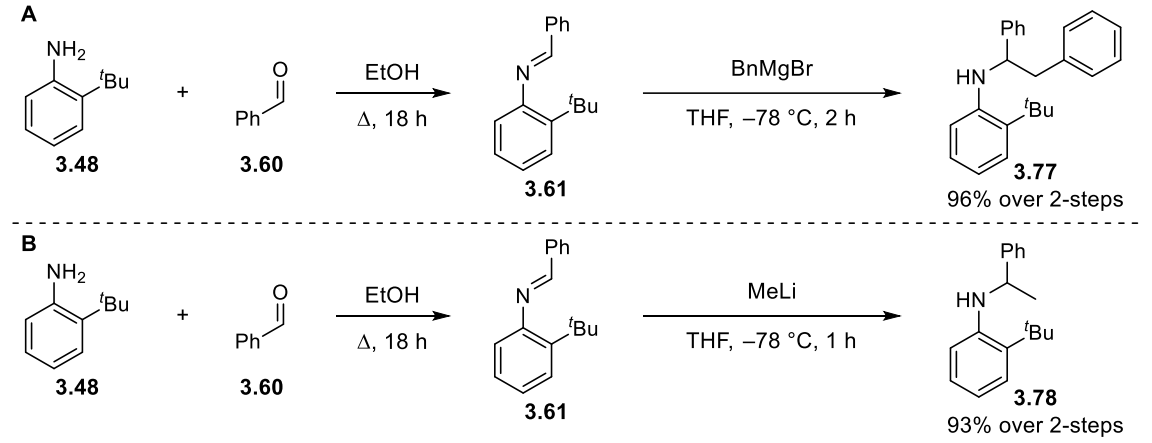
Scheme 102. [A] Synthesis of an electron rich pyridyl precursor. [B] Attempted synthesis of an electron deficient pyridyl precursor. [C] Attempted synthesis of a trifluoromethyl substituted pyridyl precursor.

Two more precursors were synthesised that were one carbon shorter, meaning that the acyl transfer process takes place through a 5-membered cyclic transition state rather than a 6-membered transition state. The first of these (Scheme 103A) was made by forming imine **3.61** in the same way as the previous example. Then, lithium halogen exchange was carried out on 2-bromopyridine **3.72** and this organolithium was reacted with imine **3.61** to form amine **3.73** in 52% yield from *tert*-butylaniline **3.48**. Again, a second precursor was synthesised with a methyl substituent in place of the phenyl group (Scheme 103B). To do this, *tert*-butylaniline **3.48** was reacted with aldehyde **3.74** to form imine **3.75**. This was then reacted with methyllithium giving the desired amine **3.76** in 91% yield over both steps.



Scheme 103. Synthesis of starting materials that proceed *via* a 5-memebered cyclic transition state.

The final two precursors that were synthesised were for the control reactions, these substrates lack the pyridyl group meaning that acyl transfer mechanism cannot take place. Both precursors were synthesised by the same method, first a condensation reaction to form imine **3.61** followed by reaction with a nucleophile. Reaction with benzylmagnesium bromide gave amine **3.77** in 96% over both steps (Scheme 104A). Reaction with methyllithium gave amine **3.78** in 93% over both steps (Scheme 104B).

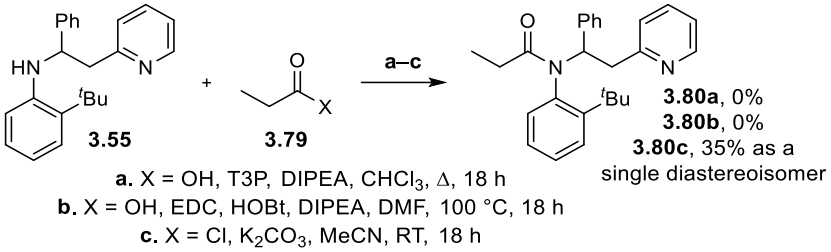


Scheme 104. Synthesis of precursors for the control reactions.

3.4 Model System

The amine precursor **3.55** was chosen to explore the feasibility of the acyl transfer reaction. Initial attempts were based on the conditions used for the ring expansion reactions presented in Chapter 2, using a carboxylic acid that was activated by T3P or EDC/HOBt (Scheme 105). In both cases there was no observation of any reaction by TLC, ^{1}H

NMR or mass spectrometry, even after heating the mixtures for 18 h. The only observable product was starting amine **3.55** with little evidence of any side products being formed. The reaction was then attempted using an acyl chloride and this gave the desired product **3.80c** in 35% yield. Pleasingly the product was isolated as a single diastereoisomer with no evidence of the minor diastereoisomer in the ^{1}H NMR of the crude reaction mixture.



Scheme 105. Initial attempts at the atroposelective acyl transfer reaction.

To identify the major diastereoisomer formed in the reaction, an X-ray crystal structure was obtained. The product of the reaction was an oil, however a solid could be obtained by reacting the product with HBF_4 to give the salt **3.81**. ^{1}H NMR of salt **3.81** showed that the product was still a single diastereoisomer and no epimerisation had occurred upon reaction with the acid. The asymmetric unit of the crystal structure is shown in Figure 8A and contains three molecules with a mixture of both enantiomers, which would mean the product crystallised with an increased enantiomeric excess. The BF_4^- anions were disordered and so could not be modelled fully; however, these were not required to assign the stereochemistry of the product. Considering one molecule from the asymmetric unit allowed the identification of the major diastereoisomer (Figure 8B), in which the phenyl substituent and *tert*-butyl group are orientated *trans*- to each other.

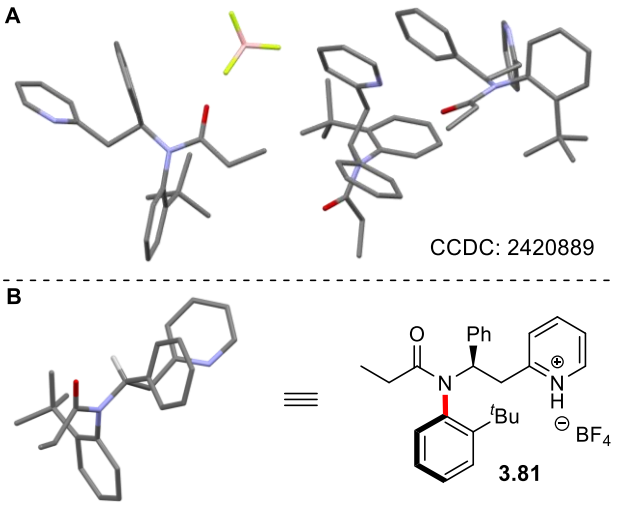


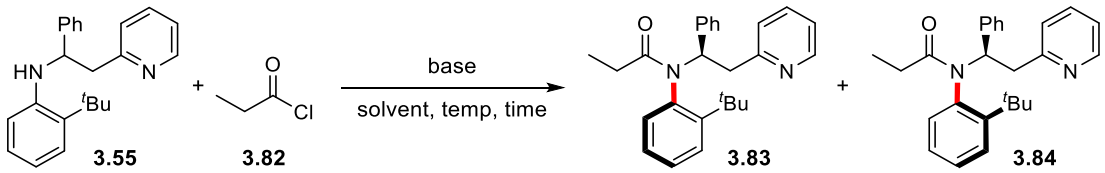
Figure 8. [A] Asymmetric unit of the crystal structure with only one BF_4^- anion shown as significant disorder prevented modelling of the remaining anions. [B] A single molecule from the asymmetric unit showing the *trans*- geometry of the phenyl and *tert*-butyl substituents.

Having shown that the reaction is possible using an acyl chloride, the reaction was optimised (Table 1). Optimisation reactions were carried out on a 0.15 mmol scale and a workup was performed to give crude reaction mixtures. The crude mixtures were analysed by ^{1}H NMR which was used to work out the ratio of starting material:product as well as the *dr*. Different solvents were screened and at room temperature (Entries 1–4) no reaction was observed, at 60 °C (Entries 5–8) some conversion was seen with chloroform and acetonitrile. In the latter case the reaction could be attempted at 80 °C (Entry 9) and this gave full conversion to the product **3.83**. Unfortunately, this result could not be replicated and when repeated gave only minor conversion to the product **3.83**, therefore further optimisation was attempted. Varying the equivalents of acyl chloride was attempted (Entries 10–14) but in all cases the conversion was <50%.

At this point it was thought that the base used could be interfering with the reaction, as triethylamine can react with acyl chlorides, potentially hindering the reaction. Different bases were screened (Entries 15–19) and all showed improved conversion. Using sodium bicarbonate (Entry 18) gave the best result with >95% conversion and a *dr* of 41:1. When no base was used (Entry 19), full conversion to the product was observed, however the *dr* dropped significantly to 9:1. This is likely because the acid generated during the reaction will protonate the pyridine, meaning only direct acylation of the aniline will take place which results in lower *dr*. This was proven by including acid at the start of the reaction (Entry 20) which showed an even lower *dr* of 3.4:1. Varying the equivalents of both the acyl

chloride and sodium bicarbonate (Entries 21–27) showed that an excess of acyl chloride (2 eq.) and sodium bicarbonate (4 eq.) gave the best conversion and *dr* (Entry 23). The reaction was found to be complete within 1 hour (Entry 28) with full conversion and excellent *dr* (59:1) and gave the major product in 98% yield after purification. The reaction also proceeded efficiently at room temperature (Entry 29), although it was later found that some examples require heating to 80 °C to obtain the best yield, and so all future reactions were carried out with heating.

Table 1. Reaction optimisation.

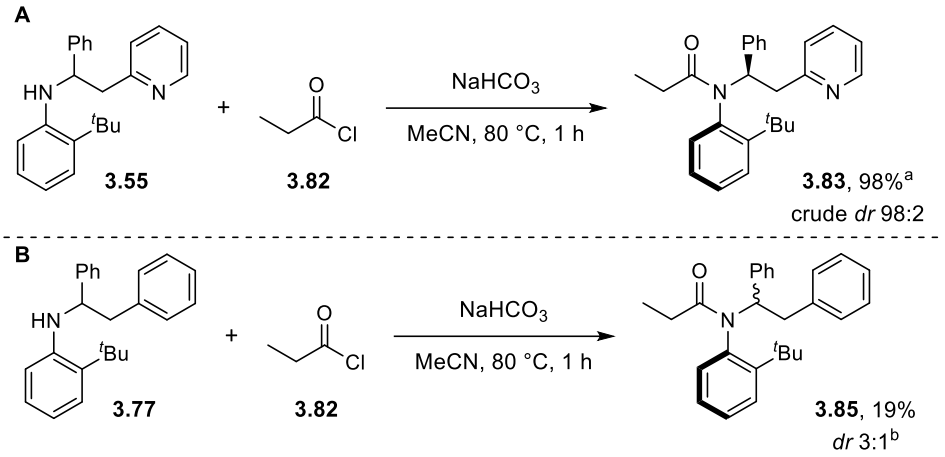


Entry	Solvent	Temp. °C	eq. of 3.82	Base	Base eq.	Conversion (3.55 : 3.83)	*dr* (3.83 : 3.84)
1	DCM	RT	4	NEt_3	4	1 : 0	-
2	$CHCl_3$	RT	4	NEt_3	4	1 : 0	-
3	benzene	RT	4	NEt_3	4	1 : 0	-
4	THF	RT	4	NEt_3	4	1 : 0	-
5	MeCN	60	4	NEt_3	4	3.6 : 1	-
6	$CHCl_3$	60	4	NEt_3	4	3.6 : 1	-
7	benzene	60	4	NEt_3	4	1 : 0	-
8	THF	60	4	NEt_3	4	50 : 1	-
9	MeCN	80	4	NEt_3	4	0 : 1[a]	-
10	MeCN	80	4	NEt_3	3	-[b]	-
11	MeCN	80	2	NEt_3	1	-[b]	-
12	MeCN	80	1	NEt_3	4	25 : 1	-
13	MeCN	80	2	NEt_3	4	2.6 : 1	-
14	MeCN	80	3	NEt_3	4	1.5 : 1	-
15	MeCN	80	4	pyridine	4	1 : 3.5	-
16	MeCN	80	4	DIPEA	4	1 : 1.6	9.3 : 1
17	MeCN	80	4	K_2CO_3	4	1 : 1.5	-
18	MeCN	80	4	$NaHCO_3$	4	1 : 26	41 : 1
19	MeCN	80	4	none	-	0 : 1	10 : 1
20	MeCN	80	2 + 2 eq. HCl	none	-	1 : 3.7	3.4 : 1
21	MeCN	80	4	$NaHCO_3$	5	1 : 18.5	44 : 1
22	MeCN	80	4	$NaHCO_3$	3	0 : 1	35 : 1
23	MeCN	80	2	$NaHCO_3$	4	0 : 1	42 : 1
24	MeCN	80	4	$NaHCO_3$	2	0 : 1	25 : 1
25	MeCN	80	1.2	$NaHCO_3$	1.5	1 : 9.2	46 : 1
26	MeCN	80	1.5	$NaHCO_3$	2	1 : 25	49 : 1
27	MeCN	80	1.5	$NaHCO_3$	3	1 : 46	44 : 1
28	**MeCN**	**80 (1 h)**	**2**	**$NaHCO_3$**	**4**	**0 : 1 (98%)[c]**	**59 : 1**
29	MeCN	RT (1 h)	2	$NaHCO_3$	4	0 : 1	114 : 1

[a] This result could not be replicated, when repeated the ratio of **3.55** : **3.83** was 8.8 : 1. [b] ^{1}H NMR signals were too broad to determine the conversion, however incomplete conversion was observed by TLC analysis. [c] Isolated yield of the major diastereoisomer.

In order to confirm the reaction proceeds *via* the proposed acyl transfer mechanism, involving acylation of the pyridyl group first then transfer to the amine, a control reaction was performed (Scheme 106). Amine **3.77** which is analogous to **3.55** but lacking the pyridyl

moiety - was reacted under the optimised reaction conditions giving the amide product **3.85** in significantly lower yield, 19% compared to 98% when the pyridyl group is present. The product was also isolated as an inseparable mixture of the two diastereoisomers with a lower *dr* of 3:1. This clearly highlights the importance of the pyridyl group in this reaction, giving both higher yield and *dr*.



Scheme 106. [A] Acylation reaction with pyridyl containing precursor **3.55**. [B] Control reaction highlighting the importance of the pyridyl group. [a] Product was isolated as a single diastereoisomer. [b] *dr* obtained from the purified material as the diastereoisomers were unable to be separated.

Atropisomers are able to undergo epimerisation upon heating as this process occurs *via* rotation of a C–N single bond. The major product **3.83** was dissolved in d^6-DMSO and first heated to 80 °C for 18 hours, showing no change in diastereomeric ratio (*dr*), indicating the product does not undergo epimerisation under the reaction conditions. The solution was then heated to 150 °C and after 7 hours had reached equilibrium with isomer **3.84** being the thermodynamically favoured diastereoisomer (Figure 9). This demonstrated that the reaction is under kinetic control, the kinetics of the equilibrium between the two diastereoisomers will be discussed later (see section 3.10).

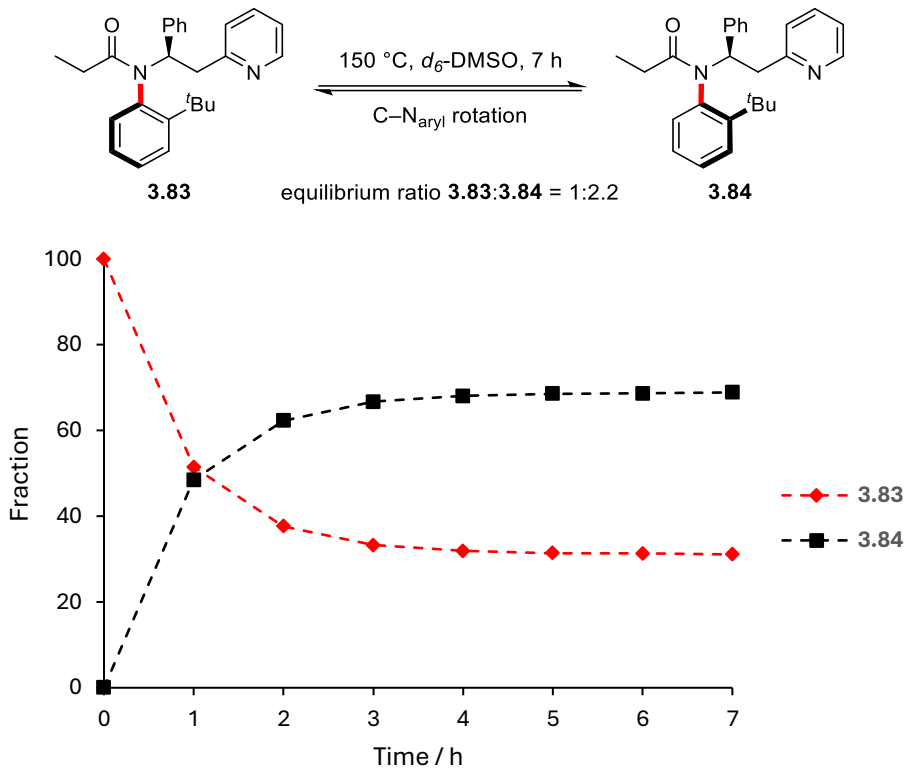
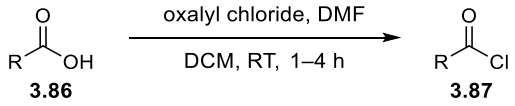


Figure 9. Thermal epimerisation of anilide **3.83**.

3.5 Reaction Scope

The acyl chlorides used for the acyl transfer were prepared following a general procedure (Scheme 107). Carboxylic acids **3.86** were stirred with oxalyl chloride and catalytic amounts of DMF which generated the desired acyl chlorides **3.87** following concentration *in vacuo*. IR spectra of the acyl chlorides were collected, confirming the reactions were complete by the absence of an OH stretch (ca. 3300 cm^{-1}). The acyl chlorides were then used in the acyl transfer reaction without further purification.



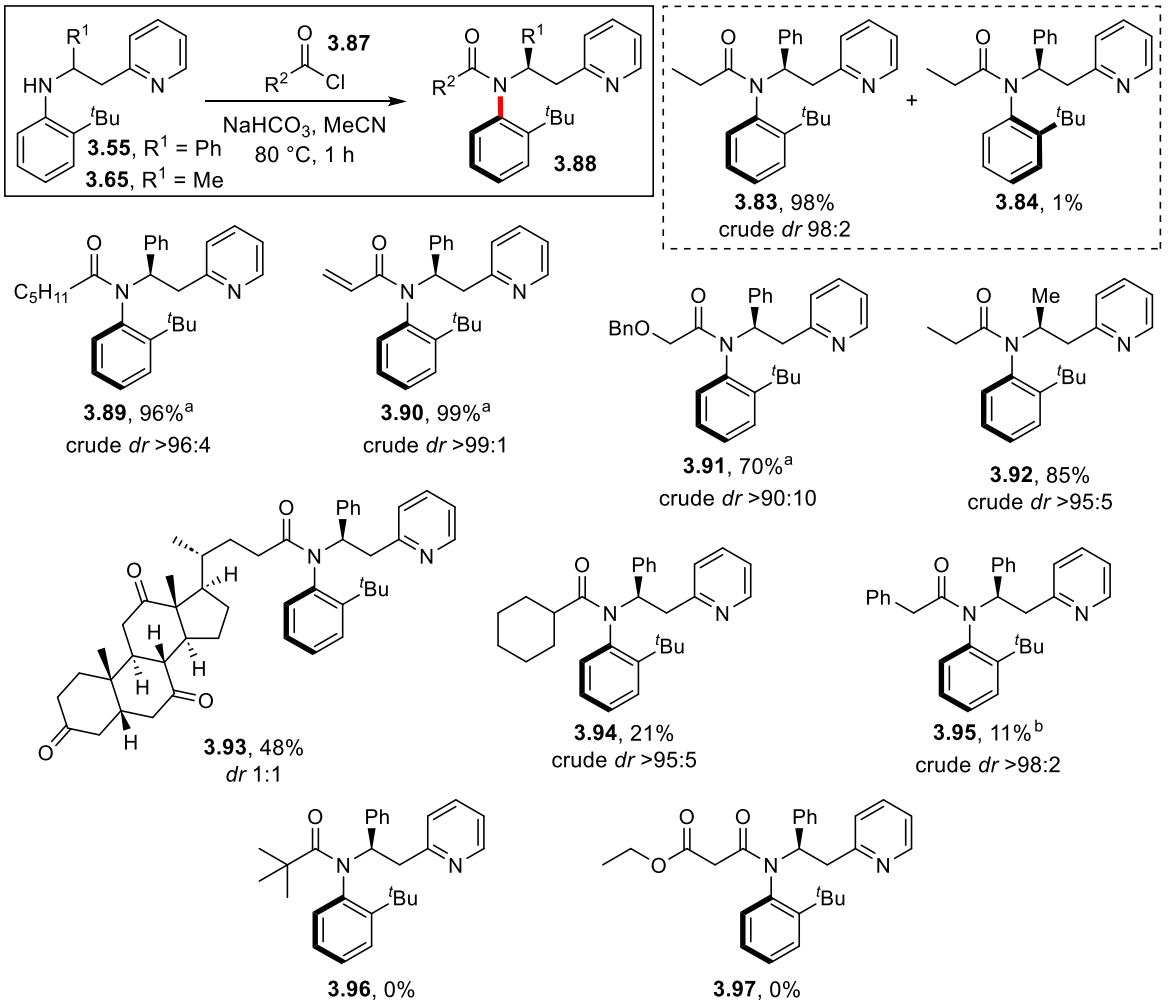
Scheme 107. General Procedure for the preparation of acyl chloride.

The scope of the reaction was first explored by changing the acyl chloride used, starting with aliphatic acyl chlorides (Scheme 108). All products were isolated as single diastereoisomers and the *dr* of the reaction was determined by analysis of the ^{1}H NMR spectra of the crude reaction mixture, before purification was carried out. This *dr* represents the ratio of the major product to the most significant minor impurity, which was

assumed to be the minor diastereoisomer. Amide **3.83**, used as the model system, had a crude *dr* of 98:2 and the major isomer was isolated in 98% yield with the minor isomer being isolated in 1% yield. This confirmed that this method of determining the *dr* was accurate. The smaller methyl substituted precursor **3.65** also gave promising results when reacted with propionyl chloride, with the product **3.92** isolated in 85% yield and a crude *dr* of >95:5, showing that smaller substituents are still sufficient to impart the stereoselectivity.

The longer chain alkyl amide **3.89** could also be isolated in high yield (96%) as well as the vinyl amide **3.90** (99%) with the *dr* for both these examples being high. The benzyl ether **3.91** had a slightly lower yield (70%) and appeared to have a slightly lower *dr* (>90:10), although the minor isomer was unable to be isolated. It was not clear why the *dr* in this reaction was lower than the other examples. In these three examples, the reactions appeared to be incomplete, by TLC analysis, after the 1 h reaction time. Therefore, after this time an extra equivalent of acyl chloride (3 eq. total) was added, and the mixtures were stirred for a further 1 hour which pushed the reactions to completion. A more complex steroid derived acyl chloride was used to synthesise amide **3.93** giving the product in 48% yield. In this case the product was isolated as a 1:1 mixture of diastereoisomers, due to the use of a chiral acyl chloride.

Not all the reactions proceeded efficiently, as was the case with cyclohexyl amide **3.94**. This product was isolated in just 21% yield, although the *dr* of the reaction appeared to remain high. This reduced yield is likely the result of increased steric hindrance, preventing the acyl transfer proceeding efficiently. This was supported by the reaction of pivaloyl chloride which showed no evidence of the formation of the desired amide **3.96**, with the starting amine remaining unchanged during the reaction. Phenylacetyl chloride was also less successful, with amide **3.95** being isolated in 11% yield. In this case, it is possible that the acidic α-proton of the acyl chloride can be deprotonated forming a ketene, which may not be able to undergo the acyl transfer reaction. When a malonate derived acyl chloride was used, the expected amide **3.97** was not observed, with the starting material remaining unreacted. This is likely due to the acidic nature of the α-proton facilitating ketene formation, and thus inhibiting acyl transfer.



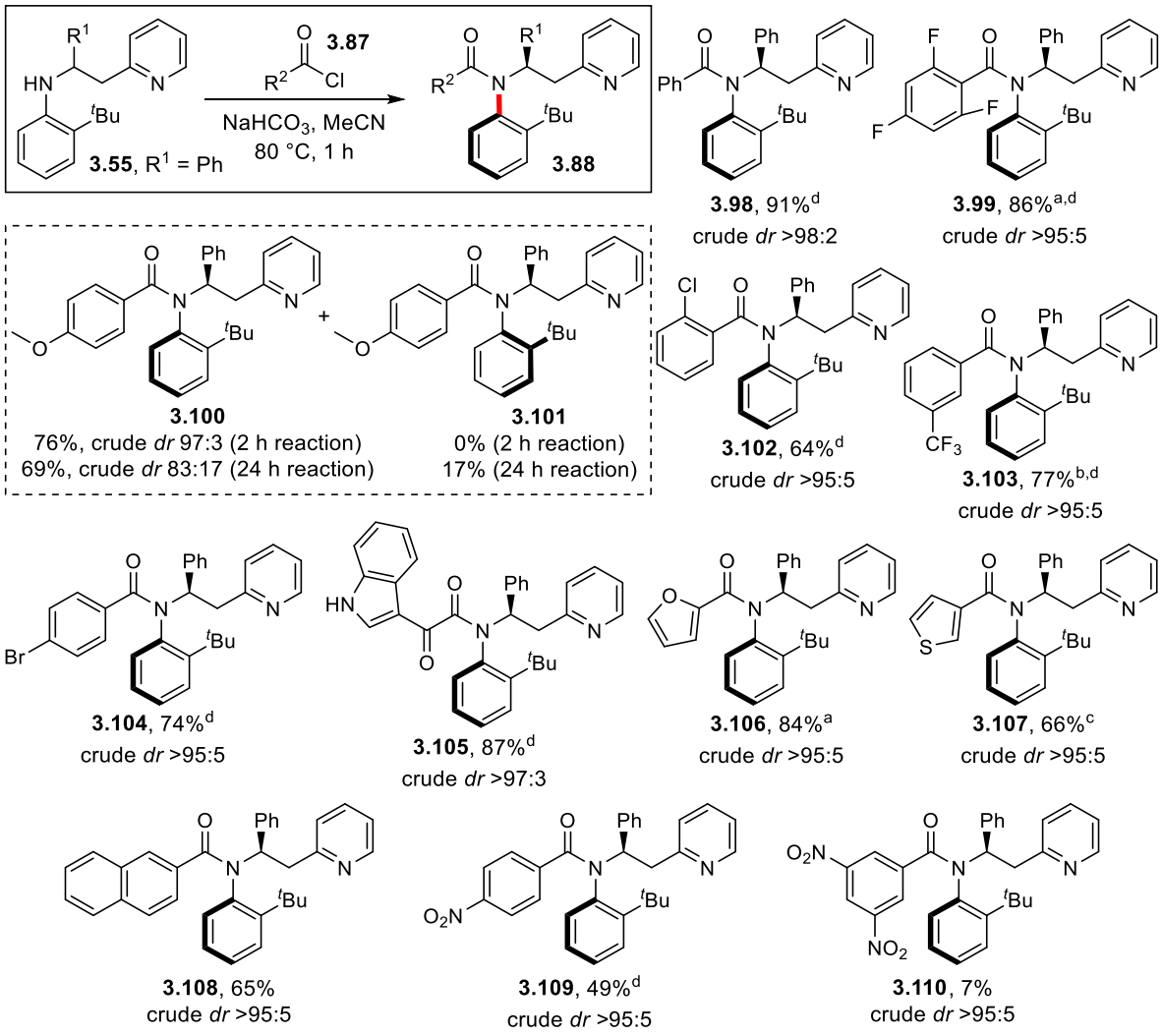
Scheme 108. Reaction scope using aliphatic acyl chlorides. [a] 3 eq. of acyl chloride and 2 h reaction time. [b] 24 h reaction time.

The reaction of aromatic acyl chlorides was also investigated and found to have a very broad scope (Scheme 109). Again, all the products in this series were isolated as single diastereoisomers. Benzoyl chloride was used first and gave the desired amide **3.98** in 91% yield with excellent crude *dr* of 98:2. Halogenated aromatics were also well tolerated, with trifluoro- (**3.99**), chloro- (**3.102**) and bromo- (**3.104**) derivatives all giving high yields with crude *dr* >95:5. Electron deficient acyl chlorides also worked well with trifluoromethyl derivative **3.103** being synthesised in 77% yield. Naphthyl derivative **3.108** was also synthesised in good yield and *dr*.

Heteroaromatic acyl chlorides could also be used in this reaction. Furan derivative **3.106** was synthesised in 84% yield while thiophene **3.107** gave slightly lower yield of 66%, both however showed high *dr* (>95:5). The unusual indoleglyoxy derivative **3.105** was also synthesised in high yield (87%). This product contains an extra carbonyl group and shows

that more complex acyl chlorides can be used to install slightly different functionalities. Nitro derivatives **3.109** and **3.110** seemed to give slightly lower yields (49% and 7% respectively) which could be due to the very strongly electron withdrawing effect, although other electron withdrawing substituents worked well (**3.99** and **3.103**). It could also be that the nitro group is causing undesirable interactions which prevent the acyl transfer taking place. In both these examples the only other major product that can be identified is the starting material **3.55**.

Electron rich acyl chlorides can also be used as was shown with methoxy derivative **3.100** which was isolated in 76% yield with a crude *dr* of 97:3 when reacted for 2 hours. When this reaction was left for 24 hours it was found that the *dr* decreased to 83:17 with the major product (**3.100b**) isolated in 69% yield and the minor isomer (**3.101b**) isolated separately in 17% yield. This decrease in *dr* is likely due to a lower barrier to rotation of the C–N_{aryl} bond, meaning epimerisation occurs when left to react for longer. No other examples were found to undergo epimerisation under the reaction conditions which suggests that electron donating aromatic groups lower the rotation barrier significantly. This finding has also been reported by other groups[106,113] and could be due to the -OMe group conjugating with the carbonyl which reduces the strength of the conjugation between the N atom and the carbonyl, thus making the N atom more sp^3-like and lowering the rotational barrier.



Scheme 109. Reaction scope using aromatic acyl chlorides. [a] 3 eq. of acyl chloride and 2 h reaction time. [b] 4 eq. of acyl chloride and 3 h reaction time. [c] 2 h reaction time. [d] 24 h reaction time. [d] Products isolated as a mixture of amide rotamers.

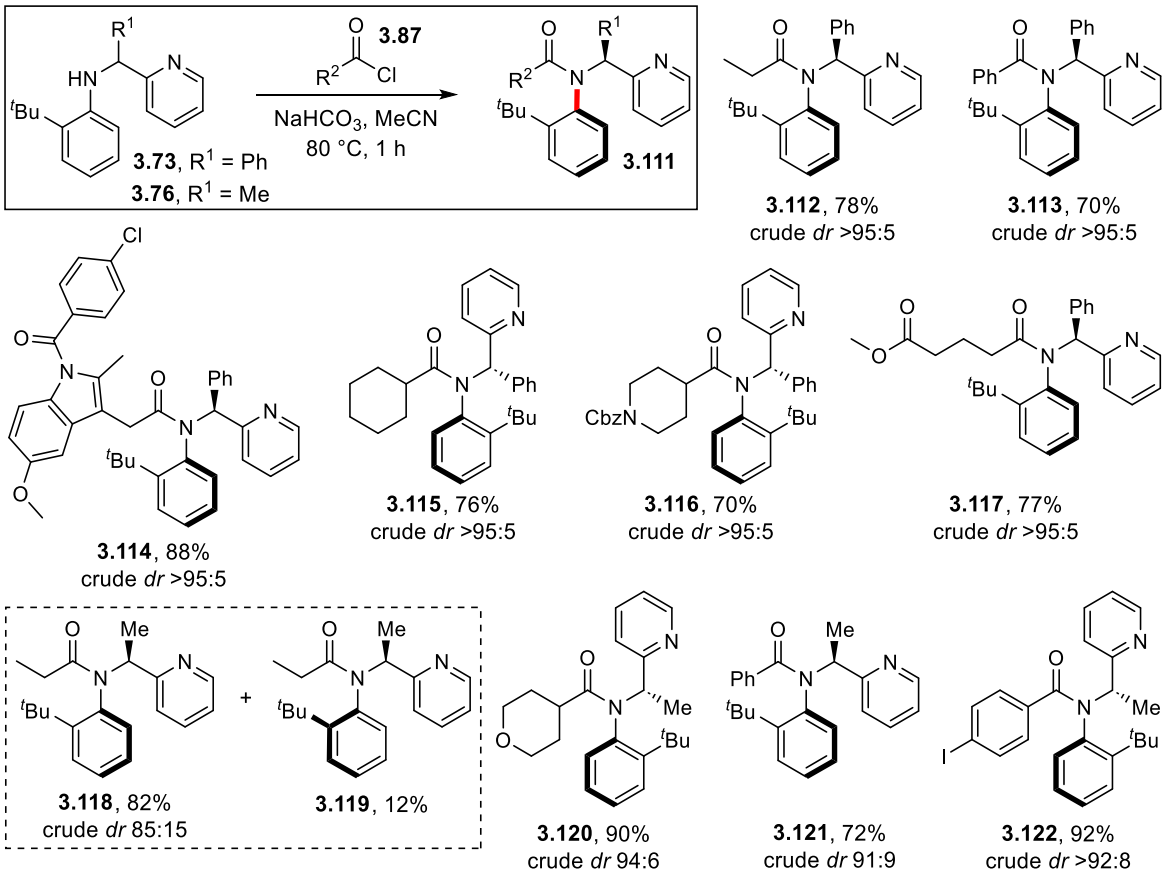
The reaction scope was then explored using precursors **3.73** and **3.76**, both of which contain one less CH_2 unit than the previous examples and so are required to proceed *via* a 5-membered transition state during the acyl transfer (Scheme 110). The reaction acyl transfer reaction proceeded efficiently using simple aliphatic and aromatic acyl chlorides to give amides **3.112**, **3.117** and **3.113** in good yields (78%, 77% and 70% respectively). In all cases the *dr*, determined from the ^{1}H NMR of the crude reaction mixtures, was found to be >95:5 which is comparable to the previous examples. More complex acyl chlorides were also compatible with amide **3.114**, which is derived from the drug indomethacin, being isolated in 88% yield.

These substrates were also more tolerant of sterically bulky acyl chlorides. For example, cyclohexyl amide **3.115** was obtained in 76% yield which represents a significant

increase in yield compared to the previous cyclohexyl amide **3.94** which was obtained in 21% yield. This difference in yield is likely due to the different conformations of the transition states, with substrate **3.73** proceeding through a 5-membered transition state whereas substrate **3.55** proceeds *via* a 6-membered transition state, meaning that in the former case there is more space to accommodate sterically bulky groups attached to the acyl chloride. *N*-Cbz protected piperidine **3.116** further demonstrated the tolerance for sterically bulky acyl chlorides by being isolated in 70% yield.

Precursor **3.76**, which contains a methyl substituent rather than a phenyl substituent, gave high yields but typically with slightly lower *dr*. this can be seen in the case of amide **3.118** which was determined to have a crude *dr* of 85:15. The two diastereoisomers were separable by column chromatography with the major diastereoisomer (**3.118**) being isolated in 82% yield and the minor (**3.119**) in 12%. This was in good agreement with the crude *dr*. The smaller methyl substituent could have lower selectivity due to having less significant steric interactions in the transition state leading to the minor isomer, meaning this pathway is more favourable then when a bulkier phenyl substituent is present.

Substrate **3.76** was also tolerant of sterically bulky acyl chloride as was demonstrated by the synthesis of tetrahydropyran **3.120** which was obtained in 90% yield. This reaction also showed a greater crude *dr* of 94:6, likely a consequence of the more sterically bulky acyl group. Finally, aromatic amides **3.121** and **3.122** were synthesised in 72% and 92% yield respectively, with both having a crude *dr* of >91:9.



Scheme 110. Reaction scope using shorter chain precursors.

Many of the products were isolated as solids which allowed crystals to be grown and X-ray crystal structures to be obtained. Three cases where crystal structures were successfully obtained are shown in Figure 10, where the hydrogen atoms have been omitted for clarity. The crystal structure of benzamide **3.98** confirmed that the stereochemistry was the same as in the model system, although as the products are racemic the opposite enantiomer crystalised in these examples. Furan **3.106** also crystalised readily and again confirmed that the stereochemistry was as expected based on the model system.

A crystal structure of amide **3.112** was also obtained which was important as this product forms through a 5-membered cyclic transition state, as opposed to a 6-membered cyclic transition state in the case of products **3.98** and **3.106**, and so there is potential for a different stereochemical outcome. Although, it was found that the major diastereoisomer **3.112** showed the expected stereochemistry based on the previous examples.

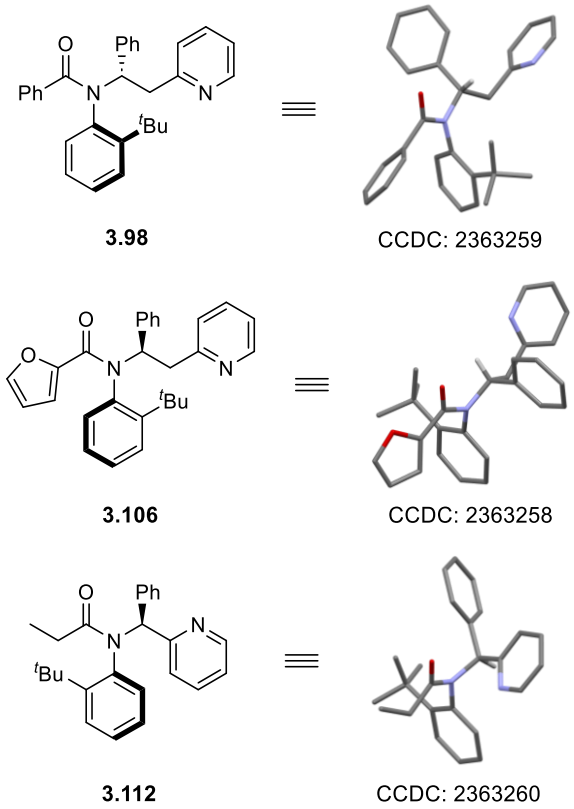
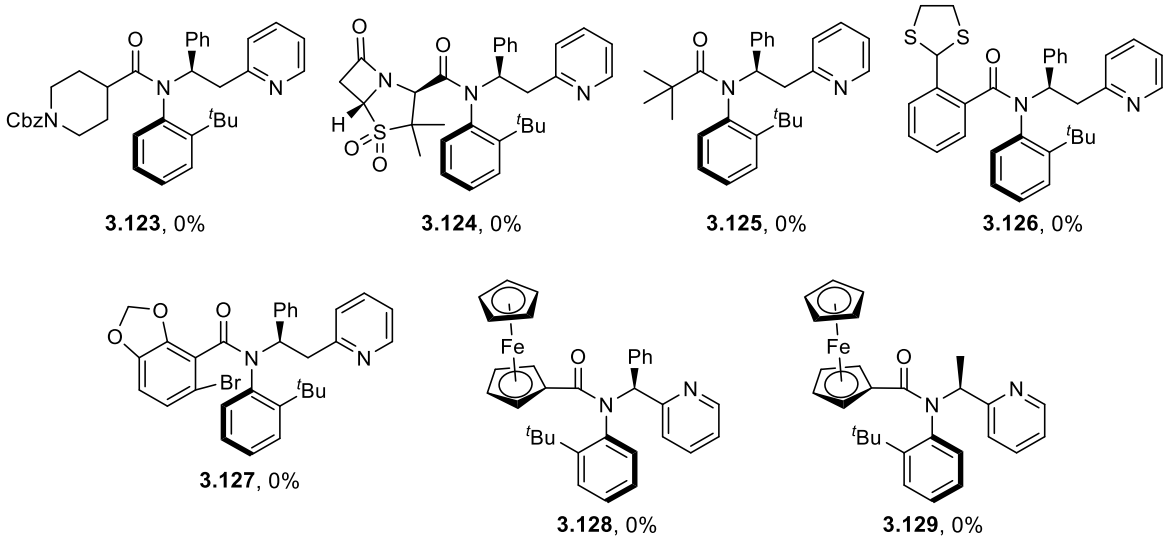


Figure 10. X-ray crystal structures to confirm the stereochemistry.

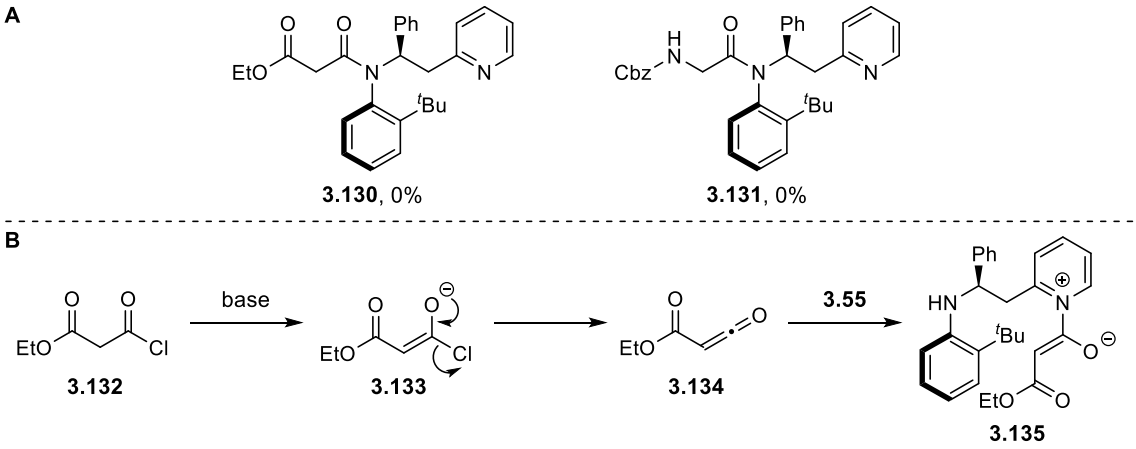
3.6 Limitations

Whilst the scope of tolerable acyl chlorides was broad, there were several examples tested that were unsuccessful with one of the main limitations being sterically bulky acyl chlorides (Scheme 111). Amides **3.123**–**3.129** were all unable to be synthesised, in each case the starting amine was the only observable product with no evidence of any reaction taking place. Amides **3.123**–**3.125** require acyl chlorides containing secondary/tertiary α-carbon atoms, whilst amides **3.126**–**3.129** require bulky *ortho*- substituted aryl acyl chlorides. In all cases it is likely that the increased bulk of the acyl chlorides result in a more sterically crowded transition state with an energy barrier that is too high to be overcome under the reaction conditions.



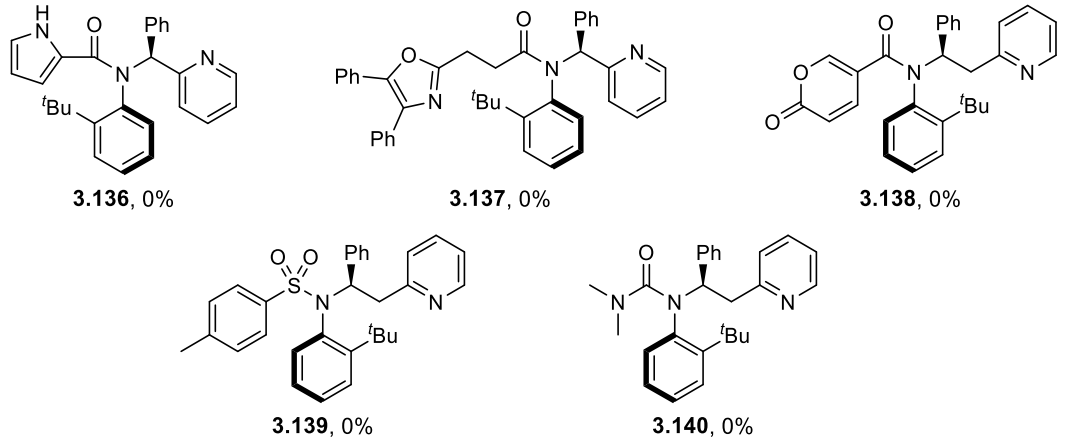
Scheme 111. Unsuccessful examples likely due to steric hinderance.

Another limitation is the use of acyl chlorides containing acidic α-protons such as those required to synthesise amides **3.130** and **3.131** (Scheme 112A). In both these cases no reaction took place with the only observable product being the unreacted starting amines. It was proposed that deprotonation of acyl chloride **3.132** could lead to enolate **3.133** which can then give ketene **3.134** (Scheme 112B). Reaction of ketene **3.134** with the pyridyl starting material **3.55** would lead to enolate **3.135**, which may remain as the enolate under the basic reaction conditions and thus cannot undergo the desired acyl transfer. Alternatively, reaction of the pyridyl starting material **3.55** with acyl chloride **3.132** could take place first, which is then followed by deprotonation to give the unreactive enolate **3.135**.



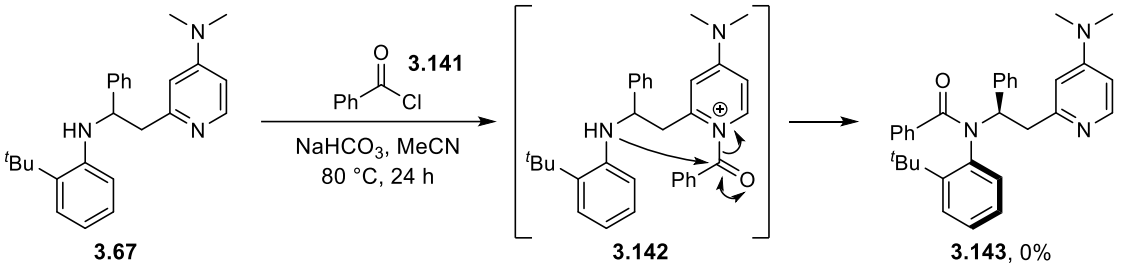
Scheme 112. [A] Unsuccessful examples likely due to ketene formation. [B] Mechanism for the formation of a ketene from an acyl chloride.

There were also examples where it was not fully clear why the reaction was unsuccessful such as in the cases of amides **3.136**–**3.138** (Scheme 113). It is possible that in these cases the acyl chlorides decompose before the desired acyl transfer mechanism can take place. An attempt to synthesise sulfonamide **3.139** and urea **3.140** were also unsuccessful with no reaction taking place. Due to the different reactivity of the sulfonyl chloride and carbamoyl chloride reagents, compared to acyl chlorides, it is possible that these products could be synthesised under different reaction conditions, although no attempt was made to optimise these reactions here.



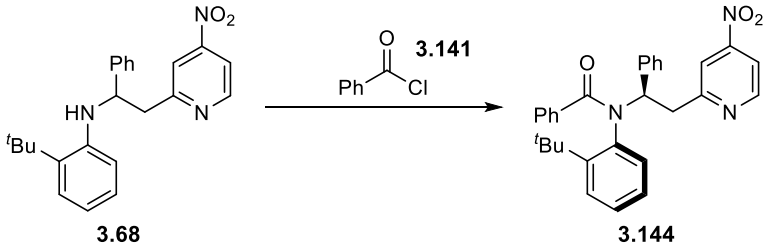
Scheme 113. Unsuccessful examples.

The reaction was also attempted using substituted pyridine **3.67** which is analogous to the commonly used nucleophilic catalyst DMAP (Scheme 114). This reaction showed no evidence of product formation even after 24 hours. This was unexpected, as it was initially thought the electron donating *N*,*N*-dimethyl group would enhance the reaction. This is because it was expected that the inclusion of the *N*,*N*-dimethyl group would increase the rate of pyridine acylation (**3.67** → **3.142**) by increasing the electron density on the pyridine nitrogen atom. However, at the same time, this makes the substituted pyridine a worse leaving group and thus may slow down the acyl transfer step (**3.142** → **3.143**), which is thought to be the rate determining step. This would result in an overall slower reaction and offers a plausible explanation for why no product was formed in this case.



Scheme 114. Attempted reaction using a substituted pyridine precursor.

With this in mind, it was thought that an electron deficient pyridine such as 4-nitro pyridine **3.68** would have the opposite effect (Scheme 115), by slowing down the initial acylation but speeding up the rate determining acyl transfer step, and thus the overall reaction. Unfortunately, all attempts to make the required electron deficient precursors were unsuccessful, as was outlined in section 3.3, and so this could not be explored.



Scheme 115. Proposed reaction using a 4-nitro pyridine precursor.

3.7 Amide Rotamers

In a small number of examples, two sets of peaks were observed in the ^{1}H NMR spectra of the purified products. This can be seen clearly by looking at the NH (highlighted red) shift of indole **3.105** which shows two peaks in a 2.30:1.00 ratio (Figure 11A). At first glance this appeared to be two diastereoisomers, meaning the reaction was not selective, however when a ^{1}H NMR spectra was obtained in d_6-DMSO the ratio of the two peaks changed to 6.30:1.00 (Figure 11B). This change would not be expected if the two peaks corresponded to diastereoisomers and therefore it was postulated that this compound exists as a mixture of amide rotamers (**3.105a** and **3.105a'**), the ratio of which could be influenced by solvent interactions. To gain further proof that these are rotamers, the d_6-DMSO solution was heated to 150 °C for 1 h as this allows epimerisation to give a mixture of the two diastereoisomers. When this was carried out, the two peaks corresponding to **3.105a** and **3.105a'** remained in the same ratio (ca. 6.30:1.00) and two new peaks were observed in a 6.66:0.79 ratio (Figure 11C). These new peaks were assigned to the

diastereoisomer **3.105b** which also exists as a mixture of two amide rotamers (**3.105b** and **3.105b'**).

Products that formed mixtures of rotamers typically contained strong electron withdrawing substituents (e.g. aromatic acyl groups bearing electron withdrawing substituents) attached to the amide group. This can be rationalised by the more electron withdrawing substituents removing electron density from the amide group, thus increasing the conjugation and sp^2 character of the nitrogen atom. This results in a higher energy barrier for rotation about the amide bond and allows the two rotameric species to be observed at room temperature.

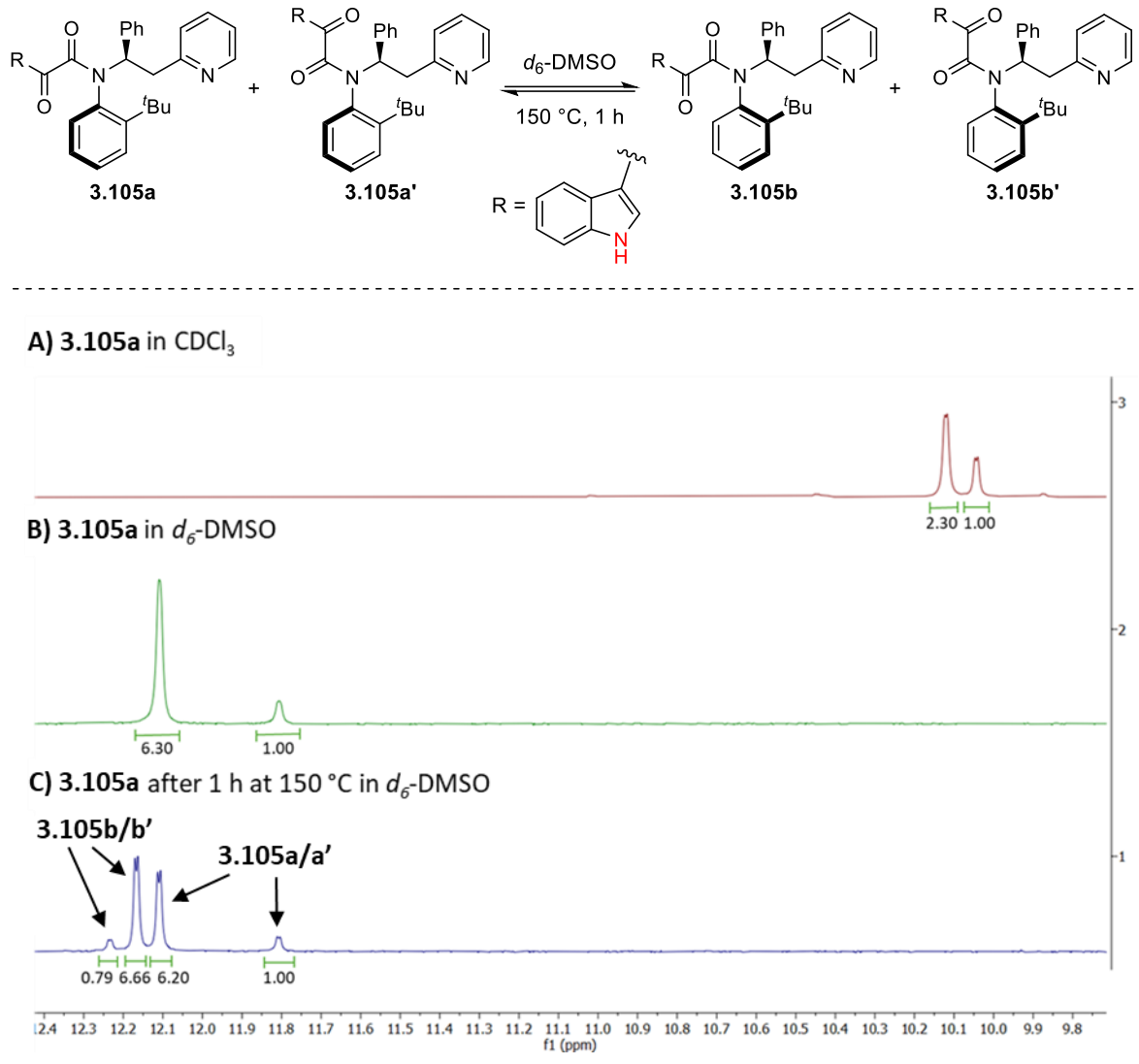
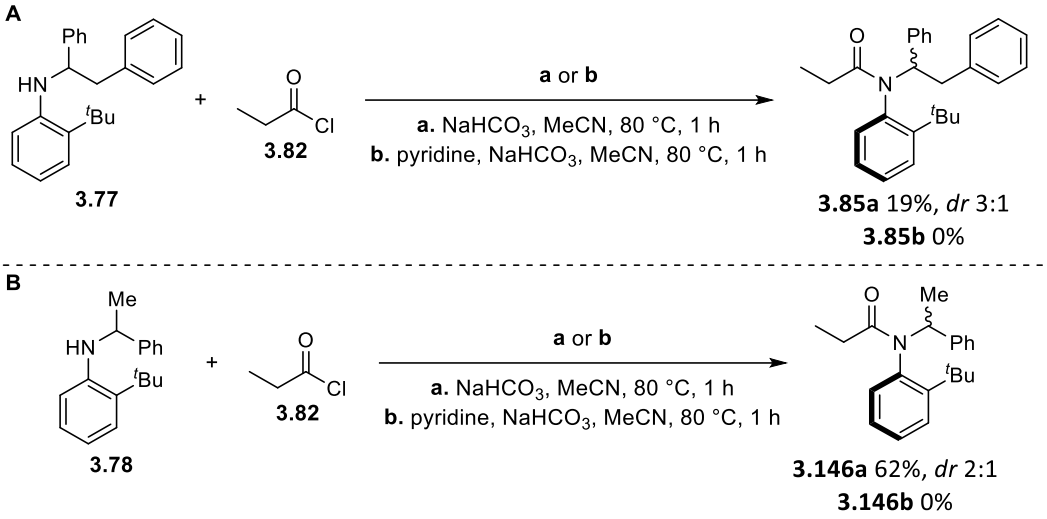


Figure 11. [A] ^{1}H NMR of **3.105a** in $CDCl_3$. [B] ^{1}H NMR of **3.105a** in d_6-DMSO. [C] ^{1}H NMR of **3.105a** in d_6-DMSO after heating to 150 °C for 1 h.

3.8 Control Reactions

As mentioned briefly in section 3.4, control reactions were performed to provide evidence for the catalytic role of the pyridyl group. The first control reaction involved the reaction of amine **3.77**, which is analogous to pyridyl substrate **3.55**, with propionyl chloride **3.82** to give amide **3.85a** in 19% yield which was isolated as a 3:1 mixture of the two diastereoisomers (Scheme 116A). This represents a significantly lower yield and *dr* compared to the pyridyl analogue **3.83**, which was isolated in 98% yield as a single diastereoisomer. A second control reaction was carried out on substrate **3.77**, this time with the inclusion of one equivalent of pyridine to explore the possibility of an intermolecularly catalysed reaction. The pyridine was expected to catalyse the reaction; however, it was unexpectedly found to hinder the reaction with no evidence of the formation of amide **3.85b**. This could potentially be due to the increased steric hindrance of the acyl pyridinium, compared to the acyl chloride, which reduced the rate of acylation of the already sterically hindered aniline. This provides strong evidence for the reaction proceeding *via* the proposed mechanism of intramolecular acyl transfer.

The same two control reactions were also performed on substrate **3.78** which is analogous to the pyridyl substrate **3.73**. Reaction with propionyl chloride **3.82** gave the amide **3.146a** in 62% as a 2:1 mixture of diastereoisomers that were inseparable by column chromatography (Scheme 116B). This was also lower yield and *dr* than the analogous pyridyl example **3.112** (82%, crude *dr* 85:15) showing that the pyridyl group is beneficial for this reaction. When pyridine was included in the reaction, no evidence for the formation of amide **3.146b** was observed by ^{1}H NMR, strongly supporting an intramolecular acyl transfer mechanism.



Scheme 116. Control reactions.

3.9 NMR Studies to Detect Reactive Intermediates

During the reaction optimisation process one reaction gave an unusual result with ^{1}H NMR spectra of the crude mixture not matching either the starting material or product. At the time this was dismissed as an anomalous result, and was therefore not included, however upon reflection it was postulated that the product observed in this reaction could be the acylated pyridinium species **3.147**. It was therefore decided to attempt to observe this intermediate to provide further evidence for the acyl transfer mechanism.

In an NMR tube, aniline **3.55** was reacted with propionyl chloride **3.82** (4 equiv.) in d_3-MeCN at room temperature and after 15 minutes a ^{1}H NMR spectrum was collected. This is shown in Figure 12C which is zoomed in on the region of the benzylic CH peak (CH highlighted in red). The spectra of starting material **3.55** and product **3.83**, in d_3-MeCN, are shown in Figure 12A and 12B respectively. From these spectra it can be seen that starting material **3.55** is rapidly consumed at room temperature and two new species can be observed that do not correspond to the starting material **3.55** or product **3.83**. ^{1}H NMR spectra (not shown) of both the staring material **3.55** and product **3.83** were obtained with the inclusion of HCl (4 equiv. from 4 M HCl in dioxane) which confirmed the new species in Figure 12C were not the result of protonation of the pyridyl moiety. These species likely correspond to intermediate acyl pyridinium **3.147** as well as the acyl pyridinium form of product **3.83**. If this is the case, these species should react with water to give a mixture of **3.55** and **3.83** in the same ratio. To test this, water (10 equiv.) and $NaHCO_3$ (5 equiv.) were then added to the NMR tube and a ^{1}H NMR spectrum was collected (Figure 12D). Pleasingly,

this led to the formation of starting material **3.55** and product **3.83** in the expected ratio, providing evidence that the species observed in Figure 12C are as proposed. The absence of the NH peak and change in splitting pattern of **3.55** in Figure 12D is likely due to the excess of water facilitating proton exchange.

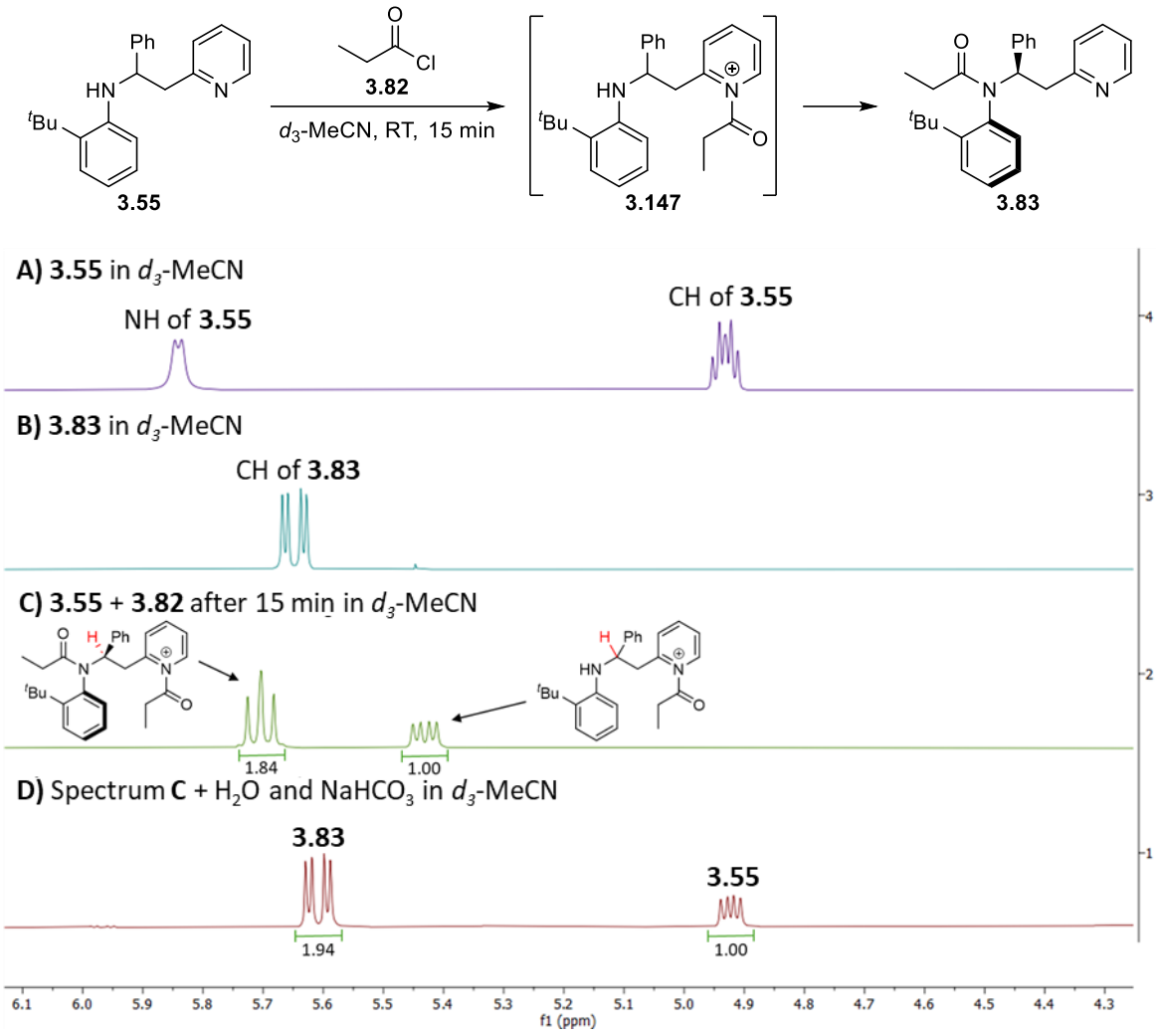


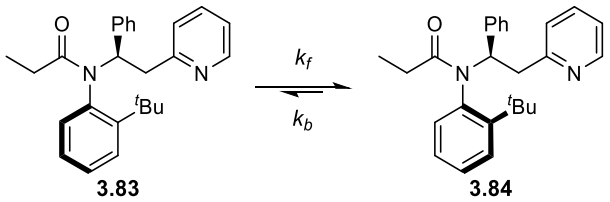
Figure 12. [A] ^{1}H NMR of **3.55** in d_3-MeCN. [B] ^{1}H NMR of **3.83** in d_3-MeCN. [C] ^{1}H NMR of a mixture of **3.55** and **3.82** in d_3-MeCN. [D] ^{1}H NMR of sample C following addition of H_2O and $NaHCO_3$ in d_3-MeCN.

3.10 Epimerisation Kinetics

Atropisomers arise from restricted rotation about a single bond due to steric factors, this means that epimerisation can take place *via* bond rotation. The degree of steric hinderance determines the energy barrier to this bond rotation and thus the rate at which epimerisation occurs. This epimerisation was investigated by heating a solution of **3.83** in d_6-DMSO to 150 °C in an NMR tube. At 1 h intervals the NMR tube was removed from the oil bath, cooled to room temperature and a ^{1}H NMR spectrum was collected before

returning the sample to the oil bath and repeating this process (7 h in total). The *dr* of the sample was determined by ^{1}H NMR and the results are shown in Table 2. This data was used to plot the time course shown in Figure 13.

Table 2. Thermal epimerisation of **3.83** at 150 °C in d_6-DMSO.



Time / h	Fraction 3.83	Fraction 3.84	$\ln([\mathbf{3.83}]_t - [\mathbf{3.83}]_{eq})$
0	1	0	–0.37
1	0.515	0.485	–1.59
2	0.377	0.623	–2.72
3	0.333	0.667	–3.82
4	0.319	0.681	–4.83
5	0.314	0.686	–5.81
6	0.313	0.687	–
7	0.311	0.689	–

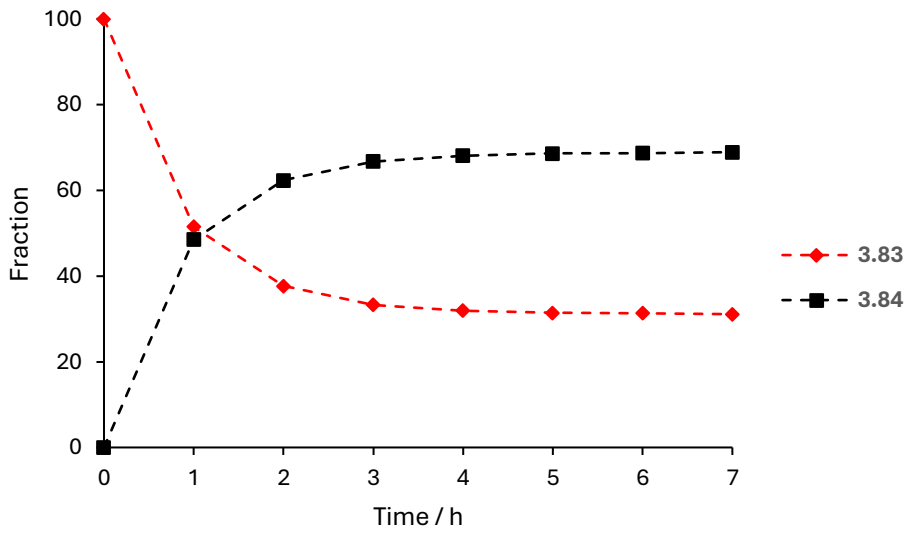


Figure 13. Thermal epimerisation plot of **3.83** at 150 °C in d_6-DMSO.

To obtain the kinetic parameters, the deviation from equilibrium *i.e.*, ln([**3.83**]$_t$–[**3.83**]$_{eq}$) was plotted against time *t* to give a straight line with a gradient of –(k_f + k_b) where [**3.83**]$_t$ and [**3.83**]$_{eq}$ are the mole fractions of **3.83** at time *t* and at equilibrium respectively

and k_f and k_b are the forward and backward rate constants respectively. This graph is shown in Figure 14.

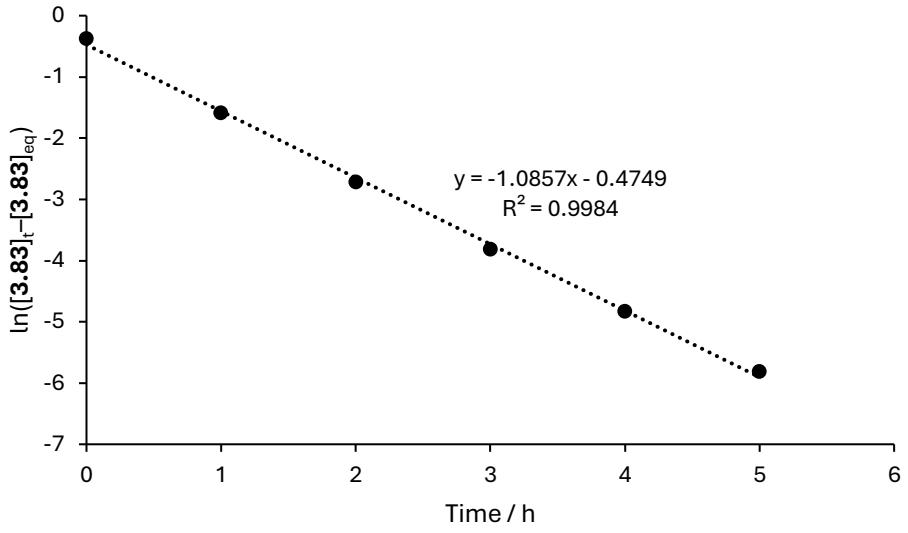


Figure 14. Plot of ln([**3.83**]$_t$–[**3.83**]$_{eq}$) vs *t* at 150 °C.

Therefore, the observed rate constant was:

$$k_{obs} = k_f + k_b = 1.086 \text{ h}^{-1}$$

Given the equilibrium ratio of **3.83**:**3.84** of 0.311:0.689 measured after 7 hours, we calculated:

$$K_{eq} = \frac{0.689}{0.311} = 2.215$$

Substituting $k_f = k_{obs} - k_b$ into $K_{eq} = \frac{k_f}{k_b}$ allowed the calculation of the backward rate constant and thus the forward rate constant:

$$k_b = \frac{k_{obs}}{K_{eq} + 1}$$

$$k_f = k_{obs} - k_b$$

k_f = 0.748 h^{-1} and k_b = 0.338 h^{-1} (at 150 °C).

The forward and backwards energy barriers ($\Delta G_f^{\ddagger}$ and $\Delta G_b^{\ddagger}$) were then calculated by substituting k_f and k_b into the Eyring equation:

$$\Delta G^{\ddagger} = -RT \ln\left(\frac{kh}{k_B T}\right)$$

$\Delta G_f^{\ddagger} = 134.7$ kJ mol^{-1} and $\Delta G_b^{\ddagger} = 137.5$ kJ mol^{-1}.

The rate constants at 25 °C can be found by substituting $\Delta G_f^{\ddagger}$ and $\Delta G_b^{\ddagger}$ into the Eyring equation:

$$k = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}}$$

k_f = 1.564 x 10^{-11} s^{-1} and k_b = 5.059 10^{-12} s^{-1} and k_{obs} = 2.070 10^{-11} s^{-1} (at 25 °C).

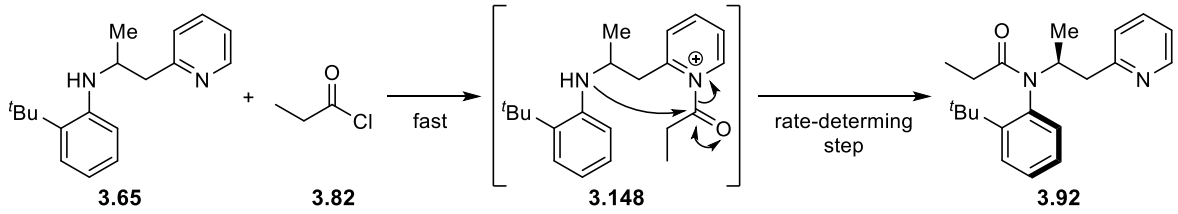
The half-life of epimerisation can then be calculated:

$$t_{1/2} = \frac{\ln 2}{k_{obs}}$$

This gives a half-life of epimerisation of 1062 years at 25 °C which clearly highlights the stability of the C–N axis, which a crucial property when considering potential applications of atropisomers *e.g.* as pharmaceutical agents.

3.11 Transition State Modelling and Thermodynamic Calculations Using DFT

Based on the failure of the DMAP analogue (Section 3.6) and the NMR studies on the reaction intermediated (Section 3.9) it was thought that pyridine acylation takes place rapidly followed by rate-determining acyl transfer to the aniline. The latter step was therefore investigated using DFT calculations to explore the selectivity of the reaction.



Scheme 117. Mechanism showing the proposed rate-determining step.

The pyridyl-acylated intermediate **A** and the two *N*-protonated atropisomers **B** and **C** were optimised at the B3LYP/6-31G* level of theory at 353 K (Figure 15). Transition states connecting **A** to **B** (**TS_{AB}**) and **A** to **C** (**TS_{AC}**) were located using the same level of theory. Intrinsic reaction coordinate (IRC) paths were calculated for the forward and backward directions which confirmed that the transition states were connected to the corresponding intermediates. The transition state **TS_{AB}** (leading to the major isomer) was found to be 42 kJ mol^{-1} lower in energy that **TS_{AC}** (leading to the minor isomer) which supports the observation that the reaction is under kinetic control.

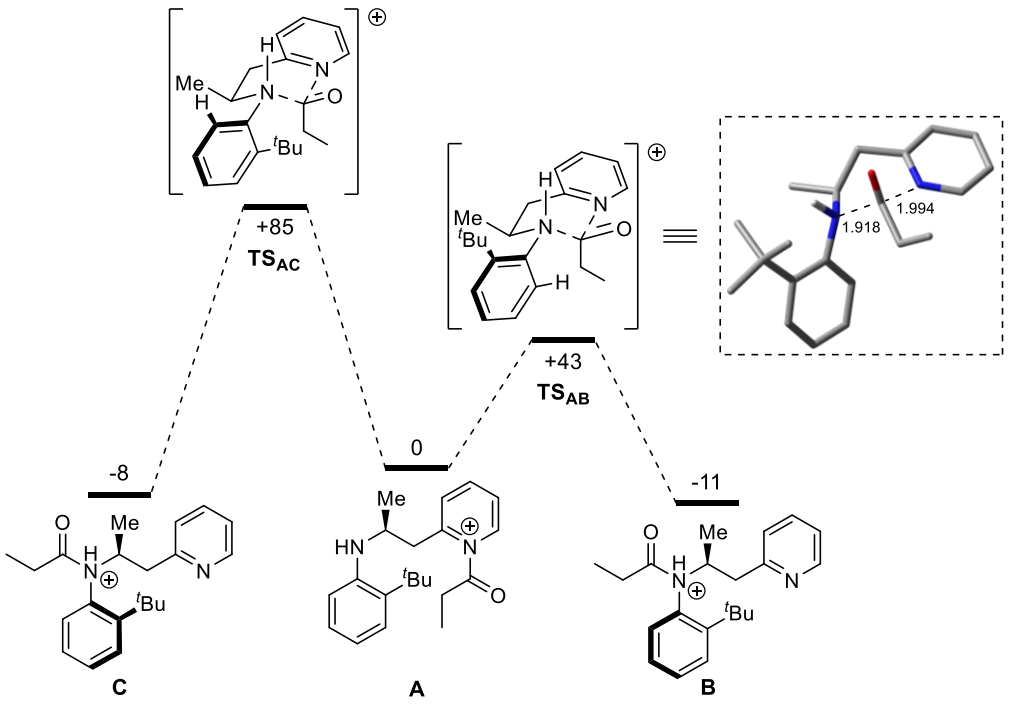


Figure 15. DFT-calculated pathway for the acyl transfer reaction. Energies are Gibbs energies in kJ mol^{-1} at the B3LYP/6-31G* level at 353 K relative to **A**. Bond lengths are in Ångstroms.

The DFT-calculated potential energy surface for the conversion of **A** to **B** and **C** was also investigated using computational various methods and show the same trends in relative energies with **TS$_{AB}$** being significantly lower in energy than **TS$_{AC}$** (Figure 16 and Table 3). IRC calculations were carried out at the five different levels of theory, confirming that each transition state is connected to the appropriate intermediates. When solvation effects, using acetonitrile as the solvent, were taken into account (Table 3, Entry 3) the *N*-protonated products **B** and **C** were found to be higher in energy than intermediate **A**. Under the reaction conditions deprotonation of intermediates **B** and **C** would likely occur rapidly to give lower energy products.

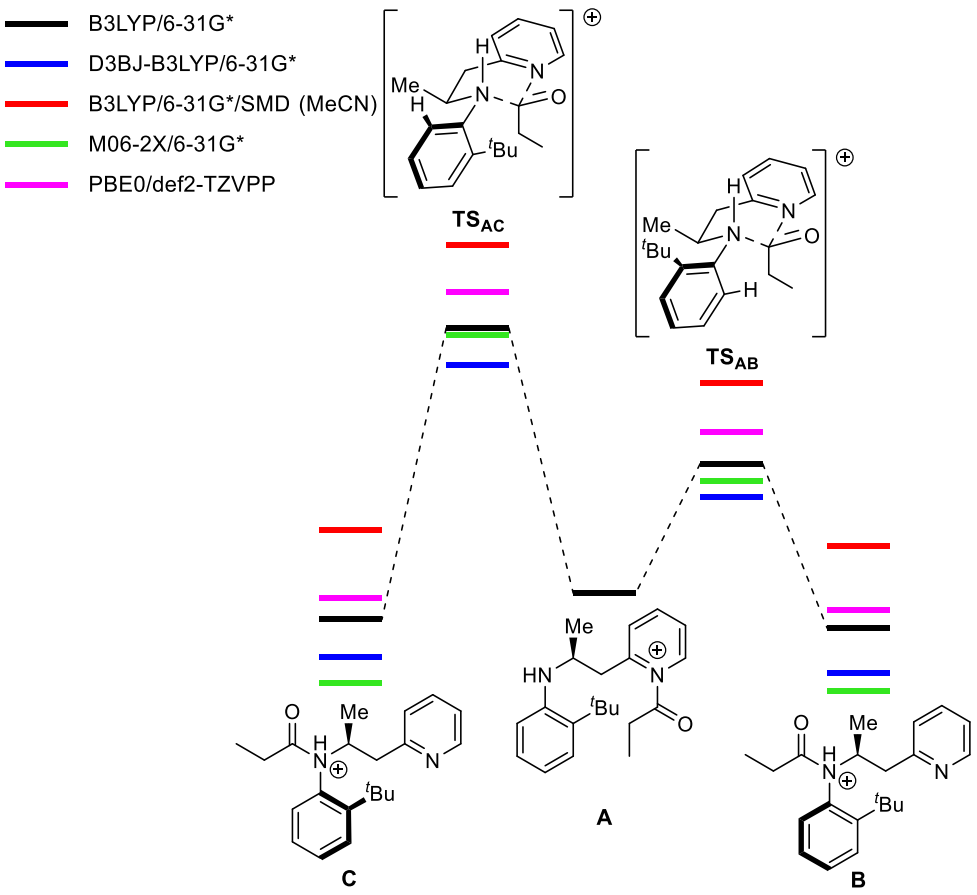


Figure 16. Relative Gibbs free energies of key intermediates and transition states at various levels of theory at 298 K.

Table 3. DFT calculated relative energies of key intermediates and transition states at various levels of theory. Energies are Gibbs free energies at 298 K in kJ mol^{-1}.

Entry	Functional	Basis Set	Solvent correction	Empirical dispersion correction	A	B	C	TS$_{AB}$	TS$_{AC}$
1	B3LYP	6-31G*	N	N	0	–12	–9	40	83
2	B3LYP	6-31G*	N	D3(BJ)	0	–24	–20	30	72
3	B3LYP	6-31G*	SMD (MeCN)	N	0	16	20	65	107
4	M06-2X	6-31G*	N	N	0	–30	–27	35	81
5	PBE0	def2-TZVPP	N	N	0	–5	–1	51	94

An interesting observation from the DFT calculated transition states is that the acyl transfer proceeds in a single step, through an S_N2-like transition state. This contrasts with the expected addition-elimination mechanism that would be expected to proceed in two steps through a tetrahedral intermediate. Initial calculations focused on an addition-elimination mechanism (Figure 17); however, the tetrahedral intermediate **D** could not be optimised to a minimum using an unconstrained optimisation. Intermediate **D** could be

optimised to a minimum only by freezing the C–O bond at 1.374 Å. When this was done, it was found that this constrained intermediate **D** is 60 kJ mol^{-1} higher in energy than the previously found S_N2 like transition state (**TS_{AB}**) and therefore the addition-elimination mechanism through a tetrahedral intermediate was ruled out.

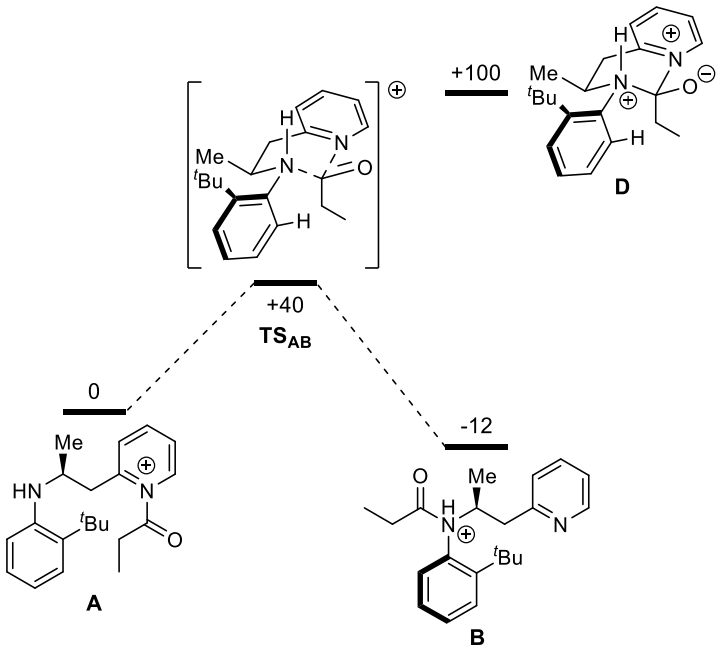
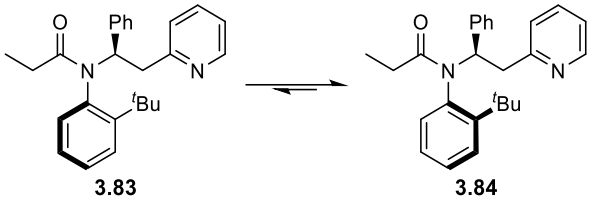


Figure 17. DFT calculated relative energies of the intermediates for an addition-elimination type mechanism vs an S_N2 like mechanism. Energies are Gibbs free energies at 298 K in kJ mol^{-1}.

The energy difference between the two diastereoisomers was also investigated using DFT calculations. The two isomers **3.83** and **3.84** were optimised at various levels of theory and the energies relative to isomer **3.83** are shown in Table 4. From this screen it can be seen that all results are in close agreement with each other, ranging from –4 kJ mol^{-1} to –9 kJ mol^{-1}, and so B3LYP/6-31G* was chosen for subsequent calculations.

Table 4. Relative energies of the two diastereomeric products using different levels of theory at 298 K. Energies are Gibbs free energies at 298 K in kJ mol^{-1}.



3.83 3.84

Entry	Functional	Basis Set	Solvent correction	Empirical dispersion correction	G_{rel} (3.83)	G_{rel} (3.84)
1	B3LYP	6-31G*	N	N	0	–6
2	B3LYP	6-31G*	N	D3(BJ)	0	–7
3	B3LYP	6-31G*	SMD (MeCN)	N	0	–4
4	B3LYP	6-31G*	SMD (DMSO)	N	0	–5
5	B3LYP	6-31G*	SMD (toluene)	N	0	–6
6	M06-2X	6-31G*	N	N	0	–9
7	PBE0	def2-TZVPP	N	N	0	–6

A range of products **3.149** prepared in the substrate scoping series were heated in an attempt to promote isomerisation to the thermodynamic atropisomer **3.150**. In total, 13 isomerically pure compounds were heated d_6-DMSO at 150 °C for 5 h. The samples were then cooled to room temperature and analysed by ^{1}H NMR to determine the *dr*. The samples were then re-heated for a further 1 hour at 150 °C, and if no change in *dr* was observed it was assumed that equilibrium had been reached. In all cases, atropisomer **3.150** was found to be the major isomer after heating, further confirming the kinetic control of the reaction. These experimentally determined equilibrium diastereomeric ratios were used to calculate the difference in free energy between the two atropisomers (ΔG_{exp}). These were compared to the DFT-calculated free energy differences (ΔG_{DFT}) and generally, ΔG_{DFT} was larger than ΔG_{exp}, although the values were within the accepted error of the calculation. In all cases the calculated and experimental results were in agreement that **3.150** is the more thermodynamically stable atropisomer. In two examples (Table 5, Entries 1 and 13) the minor diastereoisomers were isolated by column chromatography in 58% and 72% yield which allowed access to pure samples of both diastereoisomers.

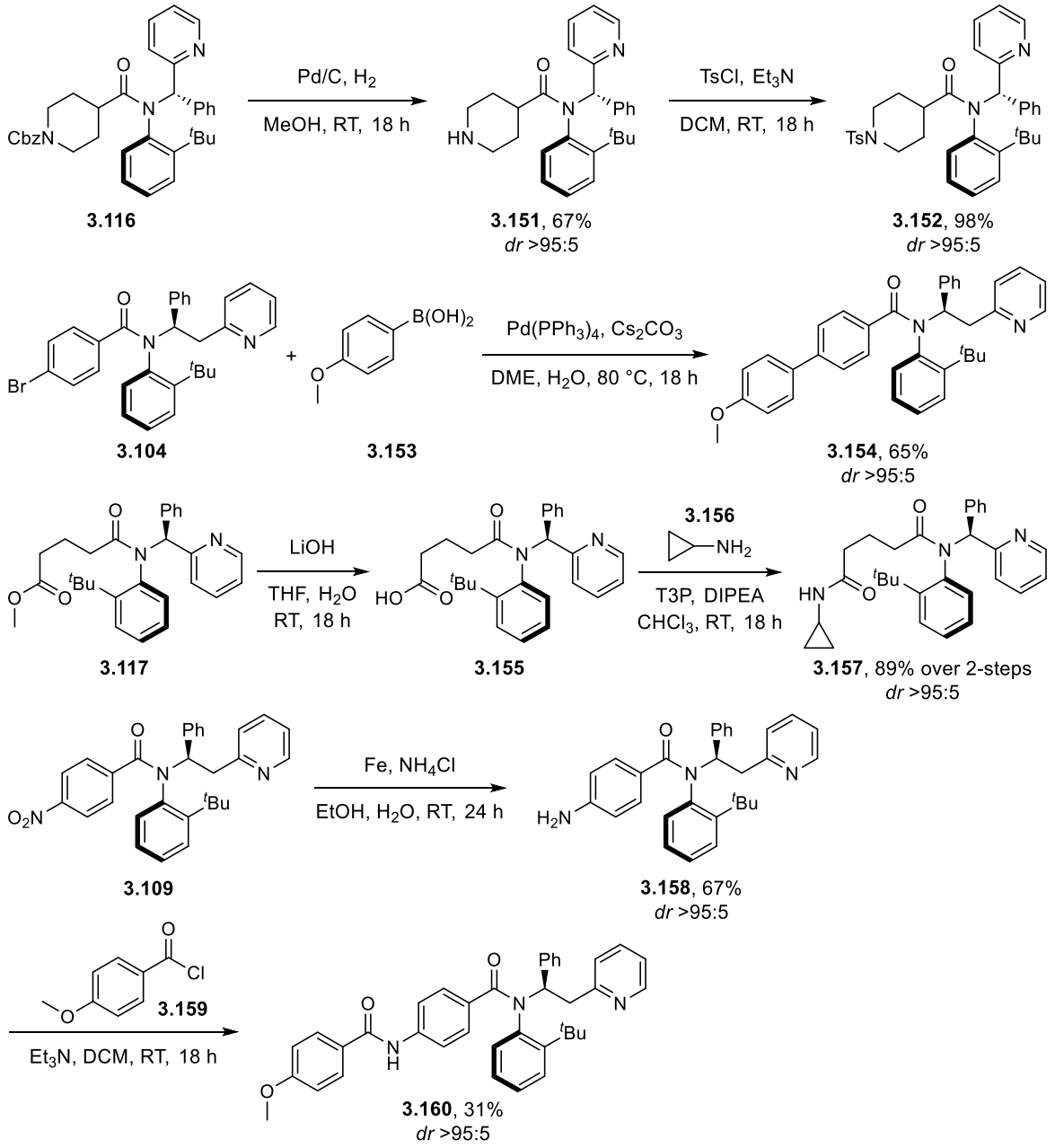
Table 5. Equilibration of atropisomers **3.149** into **3.150** upon heating to 150 °C with experimental and calculated (DFT, B3LYP/6-31G*) Δ*G* values at 150 °C.

3.149 **3.150**

Entry	R^1	R^2	n	equilibrium ratio (3.149 : 3.150)	ΔG_{exp} / kJ mol^{-1}	ΔG_{exp} / kJ mol^{-1}	isolated yield of 3.150
1	Ph	Et	1	32 : 68	2.6	5	58%
2	Ph	2-furyl	1	38 : 62	1.7	7	-
3	Ph	4-BrC_6H_4	1	40 : 60	1.4	5	-
4	Ph	2,4,6-FC_6H_2	1	32 : 68	2.6	8	-
5	Ph	4-$NO_2C_6H_4$	1	43 : 57	1.7	3	-
6	Ph	2-ClC_6H_4	1	38 : 62	1.7	7	-
7	Ph	2-naphthyl	1	42 : 58	1.2	4	-
8	Ph	4-$MeOC_6H_4$	1	43 : 57	0.9	4	-
9	Ph	3-thiophenyl	1	40 : 60	1.4	6	-
10	Me	Et	1	40 : 60	1.4	4	-
11	Ph	Et	0	27 : 73	3.5	1	-
12	Ph	Ph	0	30 : 70	3.1	1	-
13	Me	Ph	0	12 : 88	6.8	12	72%

3.12 Functionalisation Reactions

To demonstrate the utility of the anilide products, a series of functionalisation reactions were caried out (Scheme 118). Hydrogenation of Cbz protected amine **3.116** gave amine **3.151** in 67% yield which could be reacted with tosyl chloride to give sulfonamide **3.152** in 98% yield. Suzuki-Miyaura cross-coupling of bromide **3.104** was also carried out giving the biaryl product **3.154** in 65% yield without epimerisation occurring. Hydrolysis of ester **3.117** followed by amide coupling using T3P with cyclopropyl amine **3.156** gave the desired amide **3.157** in 89% yield over both steps. Reduction of nitro compound **3.109** proceeded efficiently using iron and ammonium chloride to give aniline **3.158** in 67% yield. This could then be reacted with acyl chloride **3.159** to give the amide product **3.160**, albeit in low yield of only 31%.

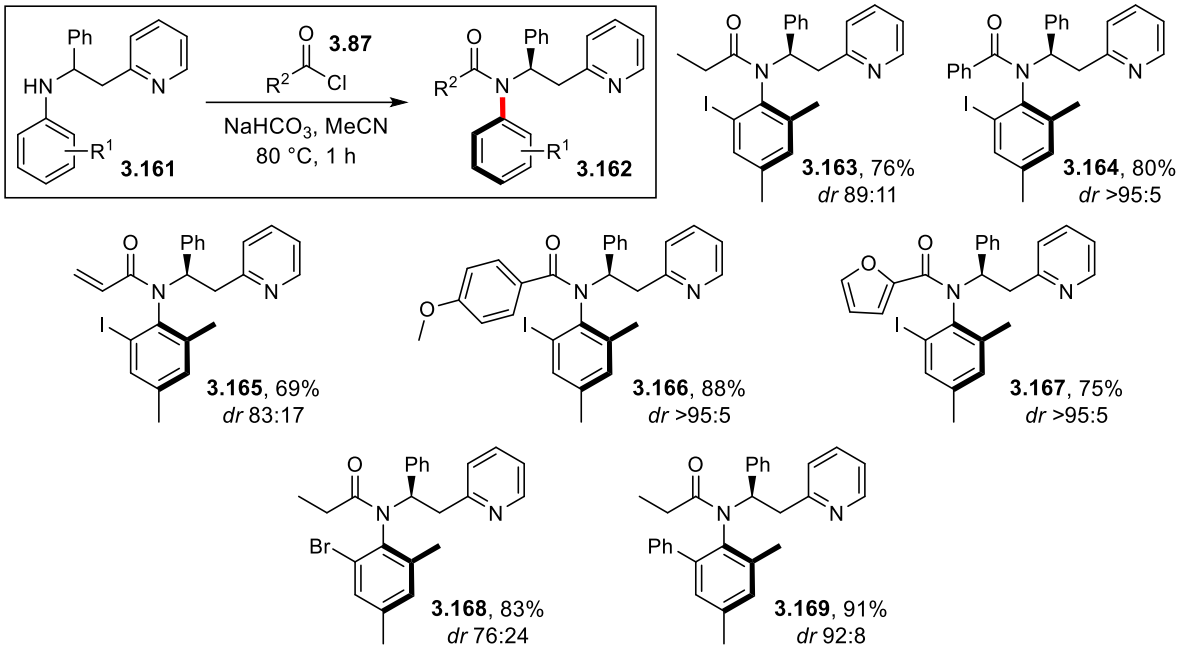


Scheme 118. Functionalisation reactions of the *tert*-butyl anilide products.

3.13 Further Scope Expansion

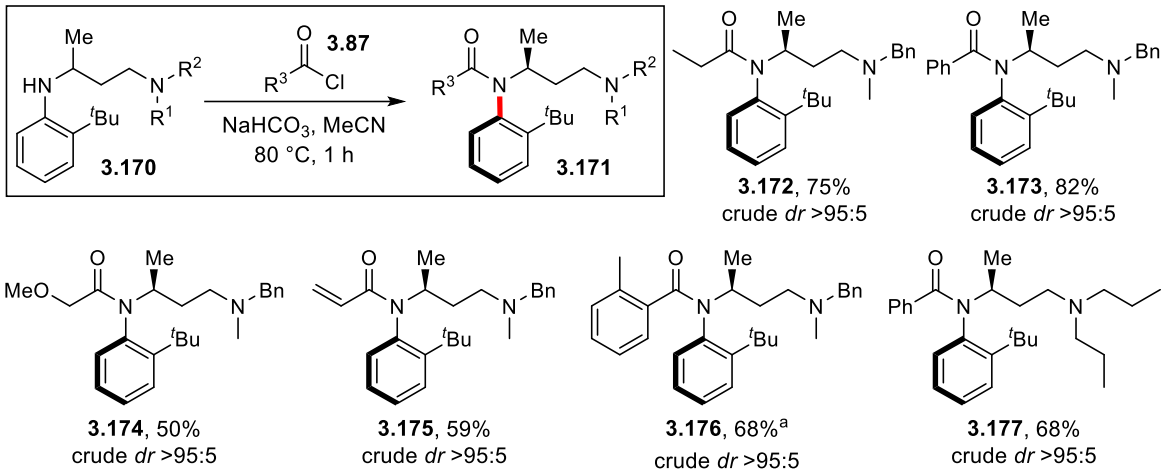
This scope of this reaction was further expanded by PhD student Natalie Roper, working under the supervision of Dr Roly Armstrong (Newcastle University). This work explored the use of substituted anilines that do not have a *tert*-butyl substituent, instead using di-*ortho*- substituted anilines (Scheme 119). Anilines bearing a methyl and iodide substituent gave amides **3.163**–**3.167** in high yields and with *dr* comparable to that of the *tert*-butyl substituted analogues. Replacing the iodide substituent with a bromide gave amide **3.168** which was obtained in high yield but with a slightly reduced *dr*. This is likely

the result of smaller steric differentiation between the methyl and bromide substituents, resulting in reduced selectivity. Using a phenyl and methyl substituted aniline also worked well, giving amide **3.169** in 91% yield with high *dr* (92:8).



Scheme 119. Exploration of tri-substituted aniline derivatives.

Master's student Catrin Morris (University of York) also expanded the scope of this reaction by exploring the use of aliphatic amines as the nucleophilic catalyst (Scheme 120). In these reactions, the tertiary amine of **3.170** is acylated first, followed by acyl transfer to the aniline to give anilides **3.171**. These reactions worked well with both aliphatic (**3.172** and **3.174**), vinyl (**3.175**) and aromatic (**3.173**, **3.176**, and **3.177**) acyl chlorides with products being isolated in 50–82% yield as single diastereoisomers. In all cases high diastereoselectivity (>95:5) was observed by ^{1}H NMR of the crude reaction mixtures, which were comparable to the pyridyl analogues.



Scheme 120. Reaction scope utilising aliphatic amines as the nucleophilic catalyst. [a] Product isolated as a mixture of amide rotamers.

3.14 Conclusion

In conclusion, a new method for the diastereoselective synthesis of chiral anilides has been developed that operates *via* an intramolecular acyl transfer from a Lewis-basic group. This method was found to be broad in scope, with all major components of the reaction being varied: the acyl chlorides, the aniline substituents and the Lewis-basic group. In most cases the reactions were high yielding and typically highly diastereoselective, with the products being easily isolable as single diastereoisomers. The two main limitations of this reaction were found to be when using sterically bulky acyl chlorides or acyl chlorides with acidic α-protons, which typically did not undergo any reaction.

These reactions were demonstrated to be under kinetic control and the products could be heated to induce epimerisation to the thermodynamically favoured isomer. In two cases this isomer was isolated by column chromatography in good yields and as a single diastereoisomers. DFT calculations also supported these observations with the calculated and experimentally determined energy differences between the two diastereoisomers matching well. Kinetic studies of the epimerisation reaction were performed and demonstrated that the products are configurationally stable at room temperature with half-lives of >1000 years.

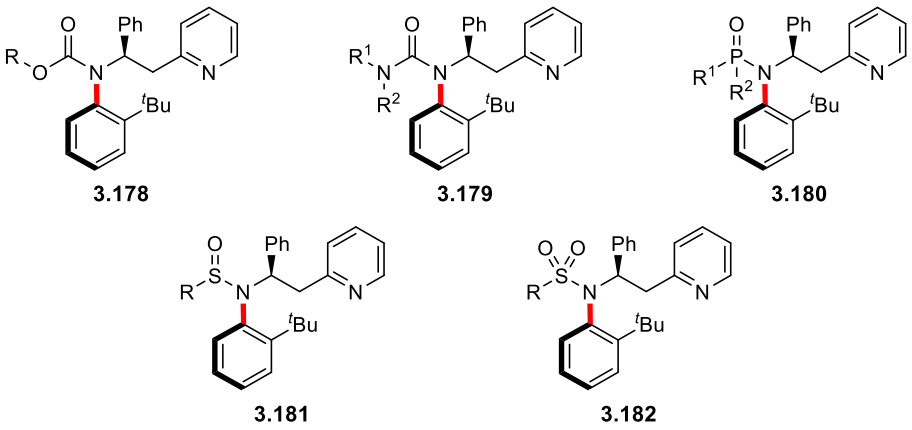
Control reactions were performed, in which the Lewis-basic group was not present, and it was found in these cases that the product was formed in significantly reduced yield and *dr*, supporting the operation *via* the proposed intramolecular acyl transfer mechanism. NMR studies of the acylated intermediates provided further evidence for this mechanism,

suggesting that rapid acylation of the Lewis-basic group is followed by rate-determining acyl transfer. The transition states for this process were modelled using DFT and were found to be in good agreement with the synthetic outcomes.

The results described in this Chapter are published in *Chemical Science*.[114]

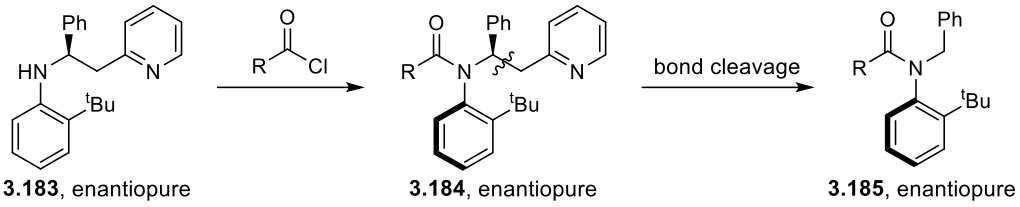
3.15 Future Work

One possibility for future work is exploring the use of alternatives to acyl chlorides. This would allow the synthesis of a range of products containing many different functional groups. For example, chloroformates would give carbamate products **3.178**, carbamoyl chlorides would give ureas **3.179**, phosphorus oxychlorides would give phoshponamides **3.180**, sulfinyl chlorides would give sulfinamides **3.181** and sulfonyl chlorides could be used to give sulfonamides **3.182**. An attempt to synthesise a sulfonamide and a urea were made but no reaction was observed and so it is likely these reactions would need significant optimisation to be viable.



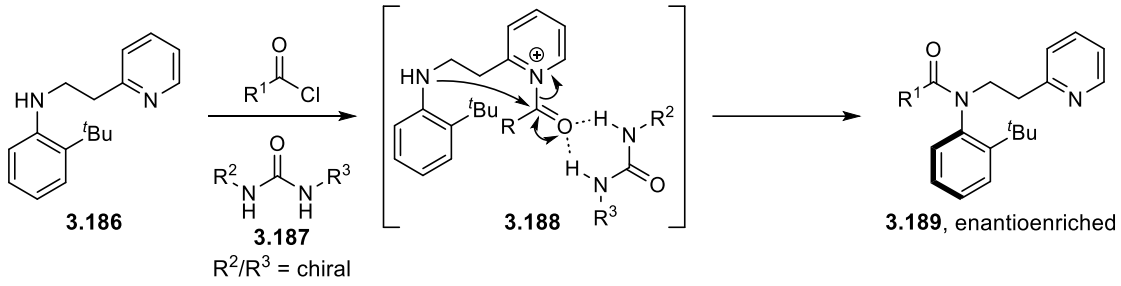
Scheme 121. Various different products that could be synthesised using alternatives to acyl chlorides.

Another interesting are to explore is the possibility of using this methodology to synthesise single enantiomers. One possible way of doing this could be a chiral auxiliary approach in which an enantiopure starting material **3.183** is synthesised, which is then subjected to the reaction conditions to give an enantiopure product **3.184**. Cleavage of the pyridyl group would result in loss of the stereogenic centre and could potentially give enantiopure atropisomers **3.185**. C–C bond cleavage in structure **3.184** is unlikely to be possible and so, for this approach to work, a new starting material would have to be designed which could undergo cleavage to remove the pyridyl group.



Scheme 122. Possible chiral auxiliary approach to access single enantiomers.

Finally, it is possible that an enantioenriched product could be synthesised using a chiral catalyst approach. Using this approach, a substrate bearing no stereogenic centre such as **3.186** could be reacted with an acyl chloride in the presence of a chiral catalyst. A potential starting point for the catalyst could be a chiral urea catalyst **3.187**, which could coordinate to the carbonyl group giving intermediate **3.188**. This coordination would likely increase the rate of reaction by making the carbonyl more electrophilic and give a diastereomeric transition state which could lead to the preferential formation of one enantiomer of product **3.189**.



Scheme 123. Possible chiral catalyst approach to access single enantiomers.

4 Experimental

4.1 General Experimental Information

Unless otherwise stated, all reactions were carried out at RT under an inert (N_2 or Ar) atmosphere in oven-dried glassware. Except where stated all reagents were purchased from commercial sources: Merck (Sigma Aldrich), Alfa Aesar, Acros Organics, Fisher Chemicals, VWR, TCI, Across chemicals and Fluorochem and were used without further purification. Anhydrous CH_2Cl_2, toluene, MeCN, Et_2O and DMF were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. Dry THF was obtained from the SPS laboratory system and used immediately after being dispensed. Dry Et_3N and DIPEA obtained by drying with CaH_2 and then distilling and storing over KOH or 3 Å molecular sieves, under Ar. Anhydrous MeOH, DMSO, acetone, ^{t}BuOH, benzene, CCl_4 and ^{n}BuOH were purchased from Sigma Aldrich and used as supplied.

^{1}H NMR spectra were recorded at 400 MHz on Bruker AV400 or Bruker AMX 400/JEOL ECS-400. ^{13}C NMR spectra were recorded at 101 MHz on Bruker AV 400 or Bruker AMX 400 MHz Ultra Shiled™. ^{19}F NMR spectra were recorded at 376 MHz on Bruker AV400 or Bruker AMX 400/JEOL ECS-400 spectrometry. ^{31}P NMR spectra were recorded at 162 MHz on Bruker AV400 or Bruker AMX 400/JEOL ECS-400 spectrometry.

All spectral data was acquired at 298 K (25 °C) unless stated otherwise and samples were dissolved in $CDCl_3$ unless specified otherwise. Chemical shifts (δ) are reported in parts per million (ppm), with residual solvent peaks: $CDCl_3$: δ_H = 7.26, $CDCl_3$: δ_C = 77.0, $(CD_3)_2SO$: δ_H = 2.50, δ_C = 39.5, CD_3OD: δ_H = 3.31, δ_C = 49.0, C_6D_6: δ_H = 7.16, δ_C = 128.1, CD_2Cl_2: δ_H = 5.32, δ_C = 53.8, $(CD_3)_2CO$: δ_H = 2.05, δ_C = 206.3, D_2O: δ_H = 4.79, $DCON(CD_3)_2$: δ_H = 8.03, δ_C = 163.2, being used for internal reference. The multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; dd, doublet of doublets; dt doublet of triplets; td, triplet of doublets; tt, triplet of triplets; ddd, doublet of doublets of doublets; where br indicates a broad signal, and app. indicates an apparent. ^{1}H experiments are reported as: chemical shift in ppm, quoted to the nearest 0.01 ppm, (integration, multiplicity, coupling constant and assignment (where possible)). ^{13}C experiments are reported as: chemical shift in ppm, quoted to the nearest 0.1 ppm, (carbon assignment (where possible) or multiplicity, coupling constant and assignment (where applicable)). ^{19}F

experiments are reported as: chemical shift in ppm, quoted to the nearest 0.1 ppm, (multiplicity, coupling constant and assignment (where possible)). ^{31}P experiments are reported as: chemical shift in ppm, quoted to the nearest 0.1 ppm, (multiplicity, and assignment (where possible)).

Assignment of compounds was achieved through use of ^{135}DEPT, COSY, HSQC and HMBC experiments. Spectra were analysed using MestReNova 12.0.3-21384 software and values of coupling constant (*J*) are reported in Hertz (Hz) to the nearest 0.5 Hz. The term "overlapping" is used to describe resonance peak, which is behind another resonance peak, *i.e*., compound resonance behind the solvent peak or combination of two resonance peaks. The systematic chemical names were generated using the IUPAC name generator tool option is included within the ChemBioDraw Ultra 19.1 software.

Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 or Pekin Elmer Spectrum 100 spectrometer fitted with a universal Attenuated Total Reflectance (ATR) accessory; data was recorded as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$, neat or solid state by ATR-FTIR. IR-recorded experiments are reported as: IR (method of recorded) ν_{max} (IR absorption maxima) / unit (cm^{-1}) chemical absorption (assignment (where possible)). The intensity of each absorbance band gives the annotated appearance, and each bond was described as w (weak), m (medium), s (strong), sh (sharp) and with the prefix v (very) and suffix br (broad).

High Resolution Mass Spectra (HRMS) were obtained by the University of York Mass Spectrometry Service, recorded on a Waters XEVO G2-XS TOF, Waters Synapt G2S TOF or Bruker Micro-TOF mass spectrometer, with HRMS mode incorporating a lock-in mass into the mobile phase (leucine enkehalin) or on a Bruker Daltonics, Micro-TOF spectrometer, using Electrospray Ionisation (ESI) or Atmospheric Pressure Chemical Ionisation (APCI), positive or negative generative modes.

Thin Layer Chromatography (TLC) was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and was visualised using UV light (λ = 254 nm, short wavelength) or UV light (λ = 366 nm, long wavelength) and stained with basic aqueous potassium permanganate ($KMnO_4$), ninhydrin or vanillin solution dip. Concentration under reduced pressure or *vacuo* was performed using a Büchi® Rotavapor® R-210 evaporator with jack and

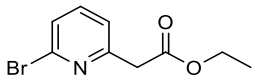
water bath, 29/32 joint, 240V rotary evaporator using a mixture of acetone and dry ice or ice/water as the coolant. Flash column chromatography was conducted using Aldrich technical grade silica gel (SiO_2), 60 Å, 230-400 mesh, 40-63 μm particle size, under a light positive pressure of air, eluting with the specified solvent system.

Melting points were recorded as decomposition temperature range and measured on a Stuart SMP10 or Gallenkamp apparatus using open tubes with no corrections. Before measuring the melting point, in most instances, the solids were purified by recrystallisation after purification by column chromatography, where "(from [solvent])" donating solvent systems were used, e.g. single or multiple.

X-ray crystallography data was collected, solved, and refined by Dr Adrian C. Whitwood or Dr Richard J. Gammons in the School of Chemistry at the University of York. Diffraction data were collected at 100 K on an Oxford Diffraction SuperNova diffractometer with Cu-K_α radiation (λ = 1.54184 Å) using a HyPix-6000HE detector. The crystal was cooled with an Oxford Instruments Cryojet. Diffractometer control, data collection, initial unit cell determination, frame integration and unit-cell refinement were carried out with CrysAlisPro, Face-indexed absorption corrections were applied using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm within CrysAlisPro. OLEX2 was used for overall structure solution, refinement and preparation of computer graphics and publication data. Within OLEX2, the algorithms used for structure solution were 'Superflip charge-flipping smtbx-flip charge-flipping ShelXT dual-spaceRefinement by full-matrix least-squares used the SHELXL algorithm within OLEX2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using a riding model and included in the refinement at calculated positions. CrystalMaker® 10 software was also used to visualise the X-ray structures with their corresponding CCDC deposit numbers given in the manuscript.

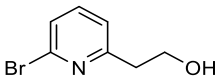
4.2 Experimental Procedures

Ethyl 2-(6-bromopyridin-2-yl)acetate (2.12)



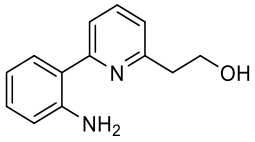
N,N-Diisopropylamine (0.840 mL, 607 mg, 6.00 mmol) was dissolved in THF (15 mL) and cooled to 0 °C before *n*-BuLi (2.40 mL, 2.5 M in hexanes, 6.00 mmol) was added dropwise and stirred for 30 mins. The mixture was cooled to –78 °C before adding 2-bromo-6-methylpyridine (0.340 mL, 516 mg, 3.00 mmol) dropwise and stirring for 30 mins. Ethyl chloroformate (0.140 mL, 163 mg, 1.50 mmol) was added dropwise and stirred for 30 mins before warming to RT. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 6.5:3.5 hexane:ethyl acetate) to yield the title compound (337 mg, 92%) as a yellow oil. R_f 0.38 (6.5:3.5 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.53 (1H, t, *J* = 8.0 Hz, ArH), 7.40 (1H, d, *J* = 8.0 Hz, ArH), 7.29 (1H, d, *J* = 8.0 Hz), 4.19 (2H, q, *J* = 7.0 Hz, OCH_2), 3.83 (2H, s, CH_2COO), 1.27 (3H, t, *J* = 7.0 Hz). Characterisation data matched those reported in the literature.[75]

2-(6-Bromopyridin-2-yl)ethan-1-ol (2.13)



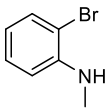
Ethyl 2-(6-bromopyridin-2-yl)acetate **2.12** (337 mg, 1.38 mmol) was dissolved in THF (14 mL) and cooled to 0 °C before adding DIBAL-H (3.00 mL, 1.0 M in THF, 3.00 mmol) dropwise. The solution was warmed to RT and stirred for 18 h. The reaction mixture was concentrated *in vacuo* and then purified by column chromatography (SiO_2, diethyl ether) to yield the title compound (218 mg, 78%) as a yellow oil. R_f 0.44 (diethyl ether); δ_H (400 MHz, $CDCl_3$) 7.48 (1H, t, *J* = 8.0 Hz, ArH), 7.35 (1H, d, *J* = 8.0 Hz, ArH), 7.15 (1H, d, *J* = 8.0 Hz, ArH), 4.01 (2H, t, *J* = 5.5 Hz, C**H**$_2$OH), 3.12 (1H, br s, OH), 3.01 (2H, t, *J* = 5.5 Hz, C**H**$_2$CH$_2$OH). Characterisation data matched those reported in the literature.[75]

2-(6-(2-Aminophenyl)pyridin-2-yl)ethan-1-ol (2.15)



A dry round-bottom flask was charged with 2-(6-bromopyridin-2-yl)ethan-1-ol **2.13** (198 mg, 0.980 mmol), 2-aminophenylboronic acid (255 mg, 1.47 mmol) and tetrakis(triphenylphosphine)palladium (57 mg, 0.049 mmol). To this was added caesium carbonate (1.60 mL, 2.1 M in water, 3.36 mmol) and 1,2-dimethoxyethane (8.2 mL) and the reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* and then ethyl acetate (25 mL) was added and washed with water (25 mL) and brine (25 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 4:1 diethyl ether:hexane) to yield the title compound (207 mg, 99%) as a brown oil. R_f 0.19 (4:1 diethyl ether:hexane); δ_H (400 MHz, $CDCl_3$) 7.64 (1H, t, *J* = 8.0 Hz, ArH), 7.48–7.43 (2H, m, ArH), 7.17 (1H, td, *J* = 8.0, 1.5 Hz, ArH), 7.02 (1H, d, *J* = 7.5 Hz, ArH), 6.81 (1H, t, *J* = 7.5 Hz, ArH), 6.73 (1H, d, *J* = 8.0 Hz, ArH), 5.48 (2H, br s, NH_2), 3.96 (2H, t, *J* = 6.0 Hz, C**H**$_2$OH), 3.01 (2H, t, *J* = 6.0 Hz, C**H**$_2$CH$_2$OH); δ_C (101 MHz, $CDCl_3$) 158.8 (ArC), 158.3 (ArC), 146.2 (ArC), 137.7 (ArC), 130.0 (ArC), 129.8 (ArC), 123.0 (ArC), 121.1 (ArC), 120.4 (ArC), 118.0 (ArC), 117.4 (ArC), 61.8 (CH_2OH), 40.2 (**C**H$_2$CH$_2$OH); v_{max}/cm^{-1} (thin film) 3317, 2924, 1610, 1588, 1450, 1311, 1240, 1158, 1042, 802, 748, 630; HRMS (ESI); calcd. for $C_{13}H_{15}N_2O^+$, 215.1179. Found: $[MH]^+$, 215.1172 (3.1 ppm error).

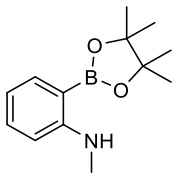
2-Bromo-*N*-methylaniline (2.19)



2-Bromoaniline (860 mg, 5.00 mmol) was dissolved in THF (5.0 mL) and cooled to –78 °C before adding *n*-BuLi (2.00 mL, 2.5 M in hexanes, 5.00 mmol) dropwise. The solution was stirred for 15 mins at –78 °C and then methyliodide (0.400 mL, 923 mg, 6.50 mmol) was added dropwise before warming to RT and stirring for 22 h. The reaction mixture was quenched with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined

organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (19:1 hexane:diethyl ether) to yield the title compound (841 mg, 90%) as a yellow oil. R_f 0.62 (19:1 hexane:diethyl ether); δ_H (400 MHz, $CDCl_3$) 7.43 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.22 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 6.64 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 6.58 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 4.36 (1H, br s, NH), 2.91 (3H, d, *J* = 5.0 Hz, CH_3). Characterisation data matched those reported in the literature.[115]

_N_-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.17)



Method A

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.10 g, 5.02 mmol) was dissolved in THF (5.0 mL) and cooled to –78 °C before adding *n*-BuLi (2.00 mL, 2.5 M in hexanes, 5.00 mmol) dropwise and stirring for 30 mins. Methyl iodide (0.310 mL, 0.710 g, 5.00 mmol) was added dropwise and the mixture was warmed to RT and stirred for 18 h. The reaction was quenched with water (10 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 19:1 hexane:ethyl acetate) to yield the title compound (299 mg, 26%) as a yellow solid. Characterisation data is given below.

Method B

To a solution of 2-bromo-*N*-methylaniline **2.19** (186 mg, 1.00 mmol) in DMF (3.5 mL) was added bis(pinacolato)diboron (508 mg, 2.00 mmol), potassium acetate (294 mg, 3.00 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (37 mg, 0.050 mmol) and the mixture was heated to 100 °C for 18 h. The reaction mixture was diluted with ethyl acetate (20 mL) and then washed with water (3 x 10 mL) and brine (3 x 10 mL). The combined aqueous layers were extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude

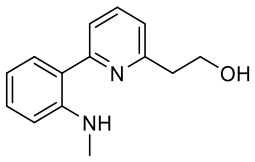
product was purified by column chromatography (9:1 hexane:ethyl acetate) to yield the title compound (82 mg, 35%) as a brown solid. Characterisation data is given below.

Method C

To a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.64 g, 7.50 mmol) in ethanol (34 mL) was added 1-(hydroxymethyl)benzotriazole (1.12 g, 7.50 mmol) and the mixture was stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo* and the product was triturated with hexane to yield the crude *N*-((1*H*-benzo[d][1,2,3]triazol-1-yl)methyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.31 g) which was used in the next step without further purification.

To a solution of *N*-((1*H*-benzo[d][1,2,3]triazol-1-yl)methyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.31 g) in THF (19 mL) was added sodium borohydride (250 mg, 6.60 mmol) and the mixture was refluxed for 1 h. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (4:1 hexane:ethyl acetate) to yield the title compound (1.28 g, 85% over 2-steps) as a white solid. R_f 0.73 (4:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.65 (1H, dd, *J* = 7.5, 2.0 Hz, ArH), 7.34 (1H, td, *J* = 7.5, 2.0 Hz, ArH), 6.64 (1H, t, *J* = 7.5 Hz, ArH), 6.57 (1H, d, *J* = 7.5 Hz, ArH), 5.80 (1H, br s, NH), 2.87 (3H, s, NCH_3), 1.35 (12H, s, $C(CH_3)_2$). Characterisation data matched those reported in the literature.[88]

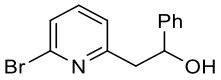
2-(6-(2-(Methylamino)phenyl)pyridin-2-yl)ethan-1-ol (2.22)



2-(6-Bromopyridin-2-yl)ethan-1-ol **2.13** (81 mg, 0.401 mmol) was dissolved in 1,2-dimethoxyethane (3.3 mL). To this was added *N*-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **2.17** (140 mg, 0.601 mmol), caesium carbonate (0.700 mL, 2.1 M in water, 1.40 mmol) and tetrakis(triphenylphosphine)palladium (23 mg, 0.020 mmol) and the reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was concentrated

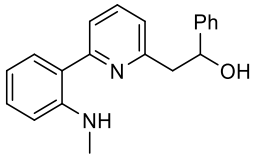
in vacuo and then ethyl acetate (10 mL) was added and washed with water (10 mL) and brine (10 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 1:1 hexane: ethyl acetate) to yield the title compound (79 mg, 87%) as a brown oil. R_f 0.28 (1:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.68 (1H, t, *J* = 8.0 Hz, ArH), 7.50 (2H, m, ArH), 7.35–7.30 (1H, m, ArH), 7.05 (1H, d, *J* = 7.5 Hz, ArH), 6.80–6.75 (1H, m, ArH), 4.03 (2H, t, *J* = 6.0 Hz, C**H**$_2$OH), 3.06 (2H, t, *J* = 6.0 Hz, C**H**$_2$CH$_2$OH), 2.92 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 159.1 (ArC), 157.8 (ArC), 148.2 (ArC), 137.6 (ArC), 130.4 (ArC), 129.6 (ArC), 122.1 (ArC), 120.7 (ArC), 120.5 (ArC), 116.0 (ArC), 110.9 (ArC), 61.8 (CH_2OH), 40.0 (**C**H$_2$CH$_2$OH), 30.1 (CH_3); ν_{max}/cm^{-1} (thin film) 3310, 2923, 1606, 1588, 1567, 1519, 1476, 1324, 1223, 1171, 1046, 750; HRMS (ESI); calcd. for $C_{14}H_{17}N_2O^+$, 229.1335. Found: $[MH]^+$, 229.1335 (0.3 ppm error).

2-(6-Bromopyridin-2-yl)-1-phenylethan-1-ol (2.23)



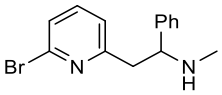
N,*N*-Diisopropylamine (3.67 mL, 2.65 g, 26.2 mmol) was dissolved in THF (60 mL) and cooled to 0 °C before *n*-BuLi (16.4 mL, 1.6 M in hexanes, 26.2 mmol) was added dropwise and stirred for 30 mins. The LDA solution was then cooled to −78 °C, where 2-bromo-6-methylpyridine (1.48 mL, 2.25 g, 13.1 mmol) was added dropwise and stirred for 30 mins. Benzaldehyde (2.67 mL, 2.78 g, 26.2 mmol) was added and stirred for a further 30 mins at −78 °C before slowly warming to RT. The solution was then quenched with sat. aq. NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 50 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 7.5:2.5 hexane:ethyl acetate → ethyl acetate) to yield the title compound (3.02 g, 83%) as a yellow oil. R_f 0.67 (50% ethyl acetate in hexanes); δ_H (400 MHz, $CDCl_3$) 7.44 (1H, t, *J* = 7.5 Hz, ArH), 7.41–7.22 (6H, m, ArH), 7.05 (1H, d, *J* = 7.5 Hz, ArH), 5.19–5.10 (1H, m, C**H**OH), 4.20–4.12 (1H, m, OH), 3.18–3.04 (2H, m, C**H**$_2$CHOH); δ_C (101 MHz, $CDCl_3$) 164.7 (ArC), 147.4 (ArC), 145.1 (ArC), 142.8 (ArC), 132.3 (ArC), 131.4 (ArC), 129.9 (ArC), 129.6 (ArC), 126.6 (ArC), 77.0 (CHOH), 49.9 (**C**H$_2$CHOH); ν_{max}/cm^{-1} (thin film) 3370, 3062, 3030, 2924, 1584,1553, 1437; HRMS (ESI); calcd. for $C_{13}H_{12}{}^{79}BrNONa^+$, 299.9994. Found: $[MNa]^+$, 299.9994 (0.3 ppm error).

2-(6-(2-(Methylamino)phenyl)pyridin-2-yl)-1-phenylethan-1-ol (2.24)



2-(6-Bromopyridin-2-yl)-1-phenylethan-1-ol **2.23** (526 mg, 1.89 mmol) was dissolved in 1,2-dimethoxyethane (16 mL). To this was added *N*-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **2.17** (663 mg, 2.84 mmol), caesium carbonate (3.20 mL, 2.1 M in water, 6.62 mmol) and tetrakis(triphenylphosphine)palladium (110 mg, 0.095 mmol) and the reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* and then ethyl acetate (50 mL) was added and washed with water (50 mL) and brine (50 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 4:1 hexane:ethyl acetate) to yield the title compound (192 mg, 33%) as a yellow oil. R_f 0.25 (4:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.69 (1H, t, *J* = 8.0 Hz, ArH), 7.53–7.49 (2H, m, ArH), 7.45–7.28 (6H, m, ArH), 7.02 (1H, d, *J* = 8.0 Hz, ArH), 6.82–6.76 (2H, m, ArH), 5.20 (1H, dd, *J* = 7.5, 5.0 Hz, CH), 3.26–3.21 (2H, m, CH_2), 2.93 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 159.1 (ArC), 157.4 (ArC), 148.1 (ArC), 143.9 (ArC), 137.9 (ArC), 130.5 (ArC), 129.8 (ArC), 128.6 (ArC), 128.5 (ArC), 127.6 (ArC), 125.9 (ArC), 121.3 (ArC), 121.0 (ArC), 116.2 (ArC), 111.1 (ArC), 73.7 (CH), 46.6 (CH_2), 30.3 (CH_3); v_{max}/cm^{-1} (thin film) 3327, 2877, 2812, 1604, 1587, 1566, 1519, 1454, 1322, 1249, 1170, 1038, 909, 799, 746, 698, 628; HRMS (ESI); calcd. for $C_{20}H_{21}N_2O^+$, 305.1648. Found: $[MH]^+$, 305.1648 (0.2 ppm error).

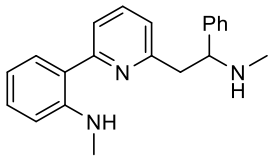
2-(6-Bromopyridin-2-yl)-*N*-methyl-1-phenylethan-1-amine (2.26)



N,N-Diisopropylamine (2.80 mL, 2.02 g, 20.0 mmol) was dissolved in THF (45 mL) and cooled to 0 °C before *n*-BuLi (8.00 mL, 2.5 M in hexanes, 20.0 mmol) was added dropwise and stirred for 30 mins. The mixture was cooled to –78 °C before adding 2-bromo-6-methylpyridine (1.10 mL, 1.72 g, 10.0 mmol) dropwise and stirring for 30 mins. *N*-benzylidenemethylamine (2.50 mL, 2.38 g, 20.0 mmol) was added dropwise and stirred for

30 mins before warming to RT. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 19:1 ethyl acetate:triethylamine) to yield the title compound (2.23 g, 77%) as a yellow oil. R_f 0.40 (19:1 ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.38–7.18 (7H, m, ArH), 6.87 (1H, d, *J* = 7.5 Hz, ArH), 4.00 (1H, dd, *J* = 8.0, 6.5 Hz, NCH), 3.14 (1H, dd, *J* = 13.5, 8.0 Hz, ArC**H**H'), 3.02 (1H, dd, *J* = 13.5, 6.5 Hz, ArCH**H'**), 2.26 (3H, s, CH_3). Characterisation data matched those reported in the literature.[75]

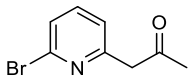
***N*-Methyl-2-(6-(2-(methylamino)-2-phenylethyl)pyridin-2-yl)aniline (2.27)**



2-(6-Bromopyridin-2-yl)-*N*-methyl-1-phenylethan-1-amine **2.26** (756 mg, 2.60 mmol) was dissolved in 1,2-dimethoxyethane (22 mL). To this was added *N*-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **2.17** (909 mg, 3.90 mmol), caesium carbonate (4.30 mL, 2.1 M in water, 9.10 mmol) and tetrakis(triphenylphosphine)palladium (150 mg, 0.130 mmol) and the reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* and then ethyl acetate (100 mL) was added and washed with water (100 mL) and brine (50 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, ethyl acetate → 19:1 ethyl acetate:triethylamine) to yield a mixture of the title compound and triphenylphosphine oxide. The triphenylphosphine oxide was removed by column chromatography (SiO_2, 19:1 diethyl ether:triethylamine) to yield the title compound (318 mg, 39%) as a yellow oil. R_f 0.50 (19:1 ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 8.29 (1H, br s, NH), 7.64–7.59 (2H, m, ArH), 7.54 (1H, d, *J* = 8.0 Hz, ArH), 7.40–7.28 (6H, m, ArH), 6.91 (1H, d, *J* = 7.5 Hz, ArH), 6.84–6.78 (2H, m, ArH), 4.10 (1H, dd, *J* = 8.0, 5.5 Hz, NCH), 3.28–3.15 (2H, m, $ArCH_2$), 3.01 (3H, s, NCH_3), 2.34 (3H, s, NCH_3), 2.01 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 159.3 (ArC), 156.7 (ArC), 148.6 (ArC), 143.2 (ArC), 137.1 (ArC), 130.3 (ArC), 129.3 (ArC), 128.4 (ArC), 127.2 (2 x ArC), 121.4 (ArC), 120.9 (ArC), 120.0 (ArC), 115.6 (ArC),

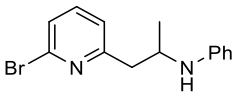
110.8 (ArC), 65.5 (NCH), 46.8 ($ArCH_2$), 34.7 (NCH_3), 30.0 (NCH_3); v_{max}/cm^{-1} (thin film) 3316, 3025, 2933, 2812, 1605, 1587, 1566, 1520, 1456, 1324, 1251, 1171, 749, 701; HRMS (ESI); calcd. for $C_{21}H_{24}N_3^+$, 318.1965. Found $[MH]^+$, 318.1968 (–1.0 ppm error).

1-(6-Bromopyridin-2-yl)propan-2-one (2.29)



A solution of *N*,*N*-diisopropylamine (11.0 mL, 10.2 g, 78.6 mmol) in dry THF (200 mL) was cooled to –78°C and to this was added *n*-BuLi (32.7 mL, 2.4 M solution in hexane, 78.6 mmol) dropwise. The resulting solution was stirred for 15 mins before adding 2-bromo-6-methylpyridine (4.44 mL, 6.76 g, 39.3 mmol) dropwise. The solution was stirred for 15 mins before adding *N*-methoxy-*N*-methylacetamide (8.73 mL, 8.11 g, 78.6 mmol). The solution was warmed to room temperature and stirred for 2 h. The reaction was quenched with water (150 mL) and extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with brine (300 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 7:3 Hexane:ethyl acetate → 6:4 hexane:ethyl acetate) to yield the title compound as a yellow oil (7.00 g, 83%); R_f 0.50 (7:3 hexane:ethyl acetate); δH (400 MHz, $CDCl_3$) 7.51 (1H, t, *J* = 8.0 Hz, ArH) 7.38 (1H, d, *J* = 8.0 Hz, ArH), 7.17 (1H, d, *J* = 8.0 Hz, ArH), 3.90 (2H, s, CH_2), 2.24 (3H, s, CH_3). Characterisation data matched those reported in the literature.[75]

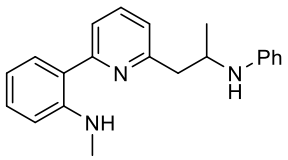
***N*-(1-(6-Bromopyridin-2-yl)propan-2-yl)aniline (2.30)**



To a solution of 1-(6-bromopyridin-2-yl)propan-2-one **2.29** (771 mg, 3.60 mmol) in 1,2-DCE (12 mL) was added aniline (0.330 mL, 335 mg, 3.60 mL), acetic acid (0.210 mL, 216 mg, 3.60 mmol) and sodium triacetoxyborohydride (1.14 g, 5.40 mmol) and the resulting mixture was stirred at room temperature for 18 h. The reaction was quenched with 1 M aq. NaOH (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 9:1 hexane:ethyl acetate) to yield the title compound (928 mg, 89%) as a yellow oil. R_f 0.25 (9:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.43 (1H,

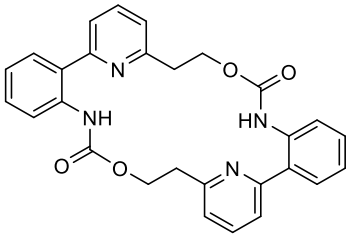
t, *J* = 7.5 Hz, ArH), 7.31 (1H, d, *J* = 8.0 Hz, ArH), 7.19–7.08 (3H, m, ArH), 6.70–6.59 (3H, m, ArH), 3.98–3.84 (2H, m, CH, NH), 3.00 (1H, dd, *J* = 13.5, 6.5 Hz, C**H**H'), 2.90 (1H, dd, *J* = 13.5, 6.0 Hz, CH**H'**), 1.22 (3H, d, *J* = 6.5 Hz, CH_3). Characterisation data matched those reported in the literature.[75]

_N_-Methyl-2-(6-(2-(phenylamino)propyl)pyridin-2-yl)aniline (2.31)



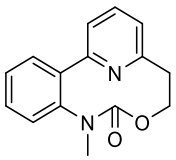
A dry round-bottom flask was charged with *N*-(1-(6-bromopyridin-2-yl)propan-2-yl)aniline **2.30** (421 mg, 1.45 mmol), *N*-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **2.17** (508 mg, 2.18 mmol) and tetrakis(triphenylphosphine)palladium (84 mg, 0.0725 mmol). To this was added caesium carbonate (2.40 mL, 2.1 M in water, 5.08 mmol) and 1,2-dimethoxyethane (12 mL) and the reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* and then ethyl acetate (30 mL) was added and washed with water (30 mL) and brine (30 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 9:1 hexane:ethyl acetate) to yield the title compound (456 mg, 99%) as a yellow oil. R_f 0.29 (9:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.73–7.66 (1H, m, ArH), 7.61–7.53 (2H, m, ArH), 7.39–7.32 (1H, m, ArH), 7.25–7.18 (2H, m, ArH), 7.06 (1H, d, *J* = 7.5 Hz, ArH), 6.82–6.67 (5H, m, ArH), 4.09–3.98 (1H, m, CH), 3.22 (1H, dd, *J* = 13.5, 5.0 Hz, C**H**H'), 2.95–2.84 (4H, m, CH**H'**, NCH_3), 1.27 (3H, d, *J* = 6.5 Hz, CHC**H**$_3$); δ_C (101 MHz, $CDCl_3$) 159.5 (ArC), 157.0 (ArC), 148.8 (ArC), 147.3 (ArC), 137.3 (ArC), 130.5 (ArC), 129.5 (ArC), 121.6 (ArC), 121.1 (ArC), 120.2 (ArC), 117.4 (ArC), 115.8 (ArC), 113.5 (ArC), 111.0 (ArC), 48.9 (CH), 43.8 (CH_2), 30.1 (NCH_3), 20.6 (CH**C**H_3); ν_{max}/cm^{-1} (thin film) 3312, 3050, 2923, 1601, 1586, 1565, 1504, 1476, 1435, 1311, 1250, 1170, 993, 745, 692, 627, 510; HRMS (ESI); calcd. for $C_{21}H_{24}N_3^+$, 318.1965. Found: $[MH]^+$, 318.1963 (0.7 ppm error).

5,12-Dioxa-3,10-diaza-1,8(2,6)-dipyridina-2,9(1,2)-dibenzenacyclotetradecaphane-4,11-dione (2.37)



To a solution of 2-(6-(2-aminophenyl)pyridin-2-yl)ethan-1-ol **2.15** (179 mg, 0.835 mmol) in DCM (17 mL) was added triethylamine (0.580 mL, 423 mg, 4.18 mmol) followed by triphosgene (87 mg, 0.292 mmol) and the resulting mixture was stirred at room temperature for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 6:4 hexane:ethyl acetate) to yield the title compound (20 mg, 10%) as a white solid. R_f 0.45 (6:4 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 10.81 (2H, s, NH), 8.28 (2H, d, *J* = 8.5 Hz, ArH), 7.71 (2H, t, *J* = 8.0 Hz, ArH), 7.52–7.43 (4H, m, ArH), 7.38–7.32 (2H, m, ArH), 7.16–7.05 (4H, m, ArH), 4.81–4.75 (4H, m, OCH_2), 3.33–3.27 (4H, m, $ArCH_2$); δ_C (101 MHz, $CDCl_3$) 157.7 (CO), 157.1 (ArC), 154.5 (ArC), 138.2 (ArC), 137.3 (ArC), 129.8 (ArC), 129.3 (ArC), 126.8 (ArC), 122.8 (ArC), 121.8 (ArC), 121.0 (ArC), 120.5 (ArC), 62.6 (OCH_2), 37.3 ($ArCH_2$); ν_{max}/cm^{-1} (thin film) 3304, 2955, 1722, 1592, 1571, 1524, 1460, 1438, 1315, 1216, 1079, 756, 733. HRMS (ESI); calcd. for $C_{28}H_{25}N_4O_4^+$, 481.1870. Found: $[MH]^+$, 481.1859 (2.3 ppm error).

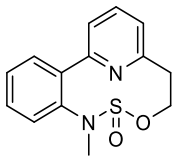
1-Methyl-4,5-dihydro-6,10-(azeno)benzo[*d*][1]oxa[3]azacyclododecin-2(1*H*)-one (2.44)



To a solution of 2-(6-(2-(methylamino)phenyl)pyridin-2-yl)ethan-1-ol **2.22** (114 mg, 0.500 mmol) and triethylamine (0.350 mL, 253 mg, 2.50 mmol) in DCM (5 mL) was added triphosgene (59 mg, 0.200 mmol) and the reaction mixture was stirred at RT for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted with DCM (3 x 20 mL).

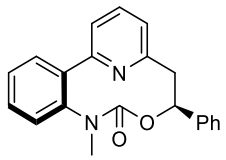
The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 10:9:1 ethyl acetate:hexane:triethylamine) to yield the title compound (75 mg, 59%) as a yellow oil. R_f 0.56 (10:9:1 ethyl acetate:hexane:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.88 (1H, d, *J* = 7.5 Hz, ArH), 7.68 (1H, t, *J* = 8.0 Hz, ArH), 7.51 (1H, d, *J* = 8.0 Hz), 7.46–7.37 (3H, m, ArH), 7.07 (1H, d, *J* = 7.5 Hz, ArH), 5.27 (1H, ddd, *J* = 12.5, 12.0, 2.5 Hz, OC**H**H'), 4.34 (1H, ddd, *J* = 12.0, 4.5, 1.5 Hz, OCH**H'**), 3.30 (1H, ddd, *J* = 17.0, 12.5, 4.5, ArC**H**H'), 2.96 (1H, ddd, *J* = 17.0, 2.5, 1.5 Hz, ArCH**H'**); δ_C (101 MHz, $CDCl_3$) 161.7 (CO), 157.0 (ArC), 153.3 (ArC), 145.4 (ArC), 137.5 (ArC), 133.0 (ArC), 131.3 (ArC), 130.5 (ArC), 128.2 (ArC), 127.7 (ArC), 120.7 (ArC), 118.4 (ArC), 66.1 (OCH_2), 39.0 (CH_3), 36.1 ($ArCH_2$); ν_{max}/cm^{-1} (thin film) 2958, 1698, 1576, 1451, 1425, 1375, 1330, 1140, 1119, 1016, 754; HRMS (ESI); calcd. for $C_{15}H_{15}N_2O_2^+$, 255.1128. Found: $[MH]^+$, 255.1129 (–0.5 ppm error).

1-Methyl-4,5-dihydro-1*H*-6,10-(azeno)benzo[*d*][1]oxa[2]thia[3]azacyclododecine 2-oxide (2.47)



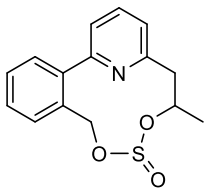
To a solution of 2-(6-(2-(methylamino)phenyl)pyridin-2-yl)ethan-1-ol **2.22** (114 mg, 0.500 mmol) and DMAP (305 mg, 2.50 mmol) in DCM (5 mL) was added thionyl chloride (0.040mL, 71 mg, 0.600 mmol) and the reaction mixture was stirred at RT for 18 h. The reaction was concentrated *in vacuo* and then purified by column chromatography (SiO_2, 11:8:1 hexane:ethyl acetate:triethylamine) to yield the title compound (63 mg, 46%) as a brown oil. R_f 0.67 (11:8:1 hexane:ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.62 (1H, t, *J* = 8.0 Hz, ArH), 7.53–7.47 (2H, m, ArH), 7.32 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 6.99 (1H, d, *J* = 7.5 Hz, ArH), 6.77–6.72 (2H, m, ArH), 4.42–4.28 (2H, m, OCH_2), 3.13 (2H, t, *J* = 6.5 Hz, $ArCH_2$), 2.92 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 159.6 (ArC), 155.1 (ArC), 148.6 (ArC), 137.5 (ArC), 130.5 (ArC), 129.5 (ArC), 121.4 (ArC), 120.7 (ArC), 120.6 (ArC), 115.7 (ArC), 110.9 (ArC), 61.3 (OCH_2), 37.9 ($ArCH_2$), 30.0 (CH_3); ν_{max}/cm^{-1} (thin film) 2921, 2813, 1605, 1587, 1566, 1519, 1559, 1326, 1251, 1205, 1172, 963, 872, 803, 748, 699; HRMS (ESI); calcd. for $C_{14}H_{15}N_2O_2S^+$, 275.0849. Found: $[MH]^+$, 275.0850 (–0.3 ppm error).

1-Methyl-4-phenyl-4,5-dihydro-6,10-(azeno)benzo[*d*][1]oxa[3]azacyclododecin-2(1*H*)-one (2.52)



To a solution of 2-(6-(2-(methylamino)phenyl)pyridin-2-yl)-1-phenylethan-1-ol **2.24** (103 mg, 0.338 mmol) and triethylamine (0.240 mL, 171 mg, 1.69 mmol) in DCM (3.4 mL) was added triphosgene (40 mg, 0.135 mmol) and the reaction mixture was stirred at RT for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product (104 mg). Compound **2.52** was unstable to column chromatography and could not be purified; therefore, to this mixture, 1,3,5-trimethoxybenzene (57 mg, 0.338 mmol) was added to determine the yield of the title compound by comparison to this internal standard (34%). The ^1H NMR signals corresponding to the product can be found at: δ_H (400 MHz, $CDCl_3$) 7.94–7.89 (1H, m, ArH), 7.74 (1H, t, *J* = 8.0 Hz, ArH), 7.63–7.28 (9H, m, ArH), 7.12 (1H, d, *J* = 8.0 Hz, ArH), 6.33 (1H, dd, *J* = 11.0, 2.5 Hz, CH), 3.44–3.21 (2H, m, CH_2), 2.89 (3H, s, CH_3); HRMS (ESI); calcd. for $C_{21}H_{19}N_2O_2^+$, 331.1443. Found: $[MH]^+$, 331.1441 (–0.5 ppm error).

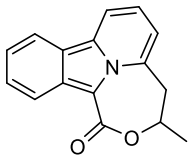
5-Methyl-5,6-dihydro-1*H*-7,11-(azeno)benzo[*e*][1,3]dioxa[2]thiacyclotridecine 3-oxide (2.65)



To a solution of 1-(6-(2-(hydroxymethyl)phenyl)pyridin-2-yl)propan-2-ol **2.35** (135 mg, 0.555 mmol) and DMAP (340 mg, 2.78 mmol) in DCM (5.6 mL) was added thionyl chloride (0.050 mL, 79 mg, 0.666 mmol) and the reaction mixture was stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 1:1 hexane:ethyl acetate) to yield the title compound (93 mg, 58%) as a 5:1 (A:B) mixture of diastereoisomer and as a white solid. R_f 0.72 (1:1 hexane:ethyl acetate); m.p. 40–44 °C; δ_H (400 MHz, $CDCl_3$) 7.72–7.60 (4H, m, ArH), 7.56–7.36 (8H, m, ArH), 7.11–7.07 (2H, m,

ArH), 6.00–5.90 (1H, m, CH isomer B), 5.48–5.38 (1H, m, CH isomer A), 5.17 (1H, d, *J* = 9.5 Hz, C**H**H'O isomer A), 5.07 (1H, d, *J* = 8.5 Hz, C**H**H'O isomer B), 4.77 (1H, d, *J* = 8.5 Hz, CH**H'**O isomer B), 4.69 (1H, d, *J* = 9.5 Hz, CH**H'**O isomer A), 3.27–3.13 (4H, m, ArC**H**$_2$CH both isomers), 1.56–1.51 (6H, m, CH_3 both isomers); δ_C (101 MHz, $CDCl_3$) 157.0 (ArC isomer A, ArC isomer B), 156.0 (ArC isomer B), 155.8 (ArC isomer A), 141.6 (ArC isomer A), 140.8 (ArC isomer B), 137.0 (ArC isomer A, ArC isomer B), 133.8 (ArC isomer A), 133.5 (ArC isomer B), 132.8 (ArC isomer B), 132.5 (ArC isomer A), 129.5 (ArC isomer A), 129.0 (ArC isomer A), 128.9 (ArC isomer B), 128.8 (ArC isomer A), 128.7 (ArC isomer B), 121.4 (ArC isomer A), 121.3 (ArC isomer B), 120.3 (ArC isomer A), 120.2 (ArC isomer B), 69.8 (CH isomer A), 68.9 (CH isomer B), 66.4 (CH_2O isomer B), 61.4 (CH_2O isomer A), 42.4 (Ar**C**H_2CH isomer B), 41.9 (Ar**C**H_2CH isomer A), 23.5 (CH_3 isomer B), 22.0 (CH_3 isomer A); ν_{max}/cm^{-1} (thin film) 2972, 2930, 1589, 1572, 1450, 1378, 1187, 1101, 1036, 908, 879, 838, 760, 728; HRMS (ESI); calcd. for $C_{15}H_{16}NO_3S^+$, 290.0845. Found: $[MH]^+$, 290.0844 (0.6 ppm error).

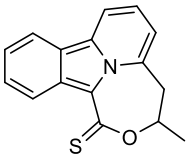
3-Methyl-3,4-dihydro-1*H*-benzo[*a*][1,4]oxazepino[3,4,5-*cd*]indolizin-1-one (2.69a)



To a solution of 1-(6-(2-(hydroxymethyl)phenyl)pyridin-2-yl)propan-2-ol **2.35** (122 mg, 0.501 mmol) and triethylamine (0.350 mL, 254 mg, 2.51 mmol) in DCM (5.0 mL) was added triphosgene (59 mg, 0.200 mmol) and the reaction mixture was stirred at RT for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 15:4:1 ethyl acetate:hexane:triethylamine) to yield the title compound (35 mg, 46%) as a yellow solid. R_f 0.43 (15:4:1 ethyl acetate:hexane:triethylamine); m.p. 135–138 °C; δ_H (400 MHz, $CDCl_3$) 8.70–8.66 (1H, m, ArH), 8.13–8.07 (2H, m, ArH), 7.64–7.58 (1H, m, ArH), 7.37–7.26 (2H, m, ArH), 7.00–6.95 (1H, m, ArH), 4.77–4.69 (1H, m, CH), 3.49–3.45 (2H, m, CH_2), 1.58 (3H, d, *J* = 6.5 Hz, CH_3); δ_C (101 MHz, $CDCl_3$) 161.6 (CO), 136.7 (ArC), 134.9 (ArC), 133.6 (ArC), 129.0 (ArC), 122.2 (ArC), 122.0 (ArC), 121.3 (ArC), 119.6 (ArC), 119.1 (ArC), 117.5 (ArC), 116.5 (ArC), 105.5 (ArC), 69.5 (CH), 42.8 (CH_2), 21.5 (CH_3); ν_{max}/cm^{-1} (thin film) 3054, 2977, 2932,

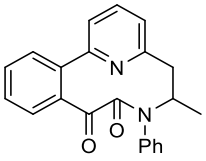
2241, 1641, 1623, 1607, 1508, 1484, 1425, 1397, 1341, 1223, 1202, 1086, 938, 751, 728, 652; HRMS (ESI); calcd. for $C_{16}H_{14}NO_2^+$, 252.1019. Found: $[MH]^+$, 252.1022 (–1.2 ppm error).

3-Methyl-3,4-dihydro-1*H*-benzo[*a*][1,4]oxazepino[3,4,5-*cd*]indolizine-1-thione (2.69b)



To a solution of 1-(6-(2-(hydroxymethyl)phenyl)pyridin-2-yl)propan-2-ol **2.35** (109 mg, 0.448 mg) and DMAP (274 mg, 2.24 mmol) in DCM (4.5 mL) was added thiophosgene (0.040 mL, 62 mg, 0.538 mmol) and the reaction mixture was stirred at RT for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (4 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 1:1 ethyl acetate:DCM) to yield the title compound (35 mg, 49%) as a dark brown solid. R_f 0.75 (1:1 ethyl acetate:DCM); m.p. 34–37 °C; δ_H (400 MHz, $CDCl_3$) 9.47 (1H, d, *J* = 8.5 Hz, ArH), 8.20–8.05 (2H, m, ArH), 7.70–7.64 (1H, m, ArH), 7.47–7.36 (2H, m, ArH), 7.05 (1H, d, *J* = 7.0 Hz, ArH), 4.90–4.82 (1H, m, CH), 3.62–3.42 (2H, m, CH_2), 1.68 (3H, d, *J* = 6.5 Hz, CH_3); δ_C (101 MHz, $CDCl_3$) 191.7 (CS), 139.9 (ArC), 136.4 (ArC), 135.9 (ArC), 130.4 (ArC), 126.0 (ArC), 124.0 (ArC), 123.7 (ArC), 122.3 (ArC), 119.3 (ArC), 119.2 (ArC), 116.8 (ArC), 116.4 (ArC), 75.5 (CH), 43.5 (CH_2), 21.7 (CH_3); v_{max}/cm^{-1} (thin film) 2925, 2854, 2208, 1713, 1670, 1637, 1605, 1507, 1479, 1407, 1395, 326, 1267, 1202, 1152, 1085, 1044, 969, 012, 756, 733; HRMS (ESI); calcd. for $C_{16}H_{14}NOS^+$, 268.0791. Found: $[MH]^+$, 268.0788 (1.1 ppm error).

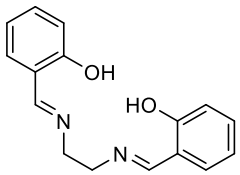
4-Methyl-3-phenyl-4,5-dihydro-1*H*-6,10-(azeno)benzo[*d*][1]azacyclododecine-1,2(3*H*)-dione (2.76)



To a solution of (2-(6-(2-(phenylamino)propyl)pyridin-2-yl)phenyl)methanol **2.33** (100 mg, 0.314 mmol) and triethylamine (0.220 mL, 159 mg, 1.57 mmol) in DCM (3.1 mL) was added triphosgene (74 mg, 0.252 mmol) and the reaction mixture was stirred at RT for 18 h. The

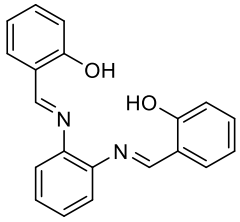
reaction was quenched with sat.aq. $NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 6:4 hexane:ethyl acetate) to yield the title compound (67 mg, 62%) as a brown solid. R_f 0.29 (6:4 hexane:ethyl acetate); m.p. 101–106 °C; δ_H (400 MHz, $CDCl_3$) 7.92–7.88 (1H, m, ArH), 7.81 (1H, t, *J* = 7.5 Hz, ArH), 7.75 (1H, d, *J* = 8.0 Hz, ArH), 7.72–7.68 (1H, m, ArH), 7.56–7.48 (2H, m, ArH), 7.34–7.25 (4H, m, ArH), 7.17 (1H, d, *J* = 7.5 Hz, ArH), 6.78–6.74 (1H, m, ArH), 5.72–5.61 (1H, m, CH), 3.09 (1H, dd, *J* = 18.0, 3.5 Hz, C**H**H'), 2.90 (1H, dd, *J* = 18.0, 11.5 Hz, CH**H'**), 1.32 (3H, d, *J* = 7.0 Hz, CH_3); δ_C (101 MHz, $CDCl_3$) 188.7 (CO), 168.9 (CO), 157.0 (ArC), 152.1 (ArC), 139.2 (ArC), 138.9 (ArC), 136.9 (ArC), 136.4 (ArC), 131.2 (ArC), 130.6 (ArC), 129.9 (ArC), 129.7 (ArC), 129.0 (ArC), 127.9 (ArC), 124.6 (ArC), 122.4 (ArC), 116.7 (ArC), 50.6 (CH), 38.9 (CH_2), 19.7 (CH_3); ν_{max}/cm^{-1} (thin film) 3064, 2973, 2934, 2246, 1667, 1634, 1593, 1567, 1492, 1450, 1414, 1203, 948, 908, 756, 725, 702, 636; HRMS (ESI); calcd. for $C_{22}H_{19}N_2O_2^+$, 343.1441. Found: $[MH]^+$, 343.1444 (–0.8 ppm error).

_N,N_'-Ethylenebis(salicylideneimine) (2.84)



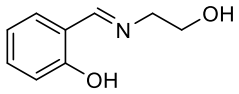
To a solution of salicylaldehyde (4.30 mL, 4.88 g, 40.0 mmol) in ethanol (80 mL) was added ethylenediamine (1.30 mL, 1.20 g, 20.0 mmol) and the resulting solution was refluxed for 5 h. The mixture was concentrated *in vacuo* and the solid was washed with ethanol to yield the title compound (4.51 g, 84%) as a yellow solid. δ_H (400 MHz, $CDCl_3$) 13.23 (2H, s, OH), 8.37 (2H, s, NCH), 7.33–7.22 (4H, m, ArH), 6.95 (2H, d, *J* = 8.5 Hz, ArH), 6.87 (2H, t, *J* = 7.5 Hz, ArH), 3.95 (4H, s, CH_2). Characterisation data matched those reported in the literature.[116]

***N*,*N*'-Bis(salicylidene)-*o*-phenylenediamine (2.86)**



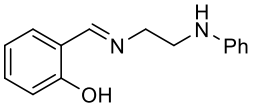
To a solution of salicylaldehyde (2.10 mL, 2.44 g, 20.0 mmol) in ethanol (74 mL) was added a solution of *o*-phenylenediamine (1.08 g, 10.0 mmol) in ethanol (50 mL) and the resulting solution was refluxed for 8 h. The mixture was concentrated *in vacuo* and the solid was washed with ethanol to yield the title compound (2.14 g, 68%) as an orange solid. δ_H (400 MHz, $CDCl_3$) 13.05 (2H, s, OH), 8.65 (2H, s, NCH), 7.41–7.33 (6H, m, ArH), 7.26–7.23 (2H, m, ArH), 7.06 (2H, d, *J* = 8.0 Hz, ArH), 6.94 (2H, t, *J* = 7.5 Hz, ArH). Characterisation data matched those reported in the literature.[117]

2-(((2-Hydroxyethyl)imino)methyl)phenol (2.88)



To a solution of salicylaldehyde (2.10 mL, 2.44 g, 20.0 mmol) in ethanol (74 mL) was added a solution of ethanolamine (1.20 mL, 1.22 g, 20.0 mmol) in ethanol (100 mL) and the resulting solution was refluxed for 3 h. The mixture was concentrated *in vacuo* to yield the title compound (3.31 g, 100%) as a yellow oil which was used without further purification. δ_H (400 MHz, $CDCl_3$) 8.39 (1H, s, NCH), 7.31 (1H, t, *J* = 8.0 Hz, ArH), 7.28–7.24 (1H, m, ArH), 6.96 (1H, d, *J* = 8.0 Hz, ArH), 6.88 (1H, t, *J* = 7.5 Hz, ArH), 3.92 (2H, t, *J* = 5.0 Hz, OCH_2), 3.75 (2H, t, *J* = 5.0 Hz, NCH_2). Characterisation data matched those reported in the literature.[118]

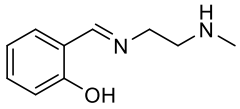
2-(((2-(Phenylamino)ethyl)imino)methyl)phenol (2.89)



To a solution of salicylaldehyde (0.530 mL, 611 mg, 5.00 mmol) in ethanol (50 mL) was added *N*-phenylethylenediamine (0.650 mL, 681 mg, 5.00 mmol) and the resulting solution was refluxed for 4 h. The mixture was concentrated *in vacuo* to yield the title compound

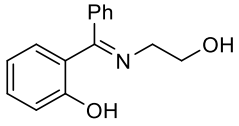
(1.17 g, 97%) as a yellow solid which was used without further purification. δ_H (400 MHz, $CDCl_3$) 8.34 (1H, s, CH), 7.37–7.31 (1H, m, ArH), 7.27–7.17 (3H, m, ArH), 6.99 (1H, d, *J* = 8.5 Hz, ArH), 6.93–6.87 (1H, m, ArH), 6.75 (1H, t, *J* = 7.5 Hz, ArH), 6.68–6.63 (2H, m, ArH), 3.84 (2H, t, *J* = 6.0 Hz, CH_2), 3.53 (2H, t, *J* = 6.0 Hz, CH_2). Characterisation data matched those reported in the literature.[119]

2-(((2-(Methylamino)ethyl)imino)methyl)phenol (2.90)



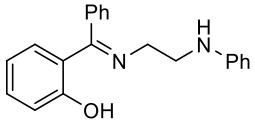
To a solution of salicylaldehyde (0.530 mL, 611 mg, 5.00 mmol) in ethanol (50 mL) was added *N*-methylethylenediamine (0.440 mL, 371 mg, 5.00 mmol) and the resulting solution was refluxed for 4 h. The mixture was concentrated *in vacuo* to yield the title compound (882 mg, 99%) as a yellow oil which was used without further purification. δ_H (400 MHz, $CDCl_3$) 8.40 (1H, s, CH), 7.35–7.24 (2H, m, ArH), 7.02–6.80 (2H, m, ArH), 3.80–3.70 (2H, m, CH_2), 2.98–2.88 (2H, m, CH_2), 2.48 (3H, s, CH_3). Characterisation data matched those reported in the literature.[120]

2-(((2-Hydroxyethyl)imino)(phenyl)methyl)phenol (2.92)



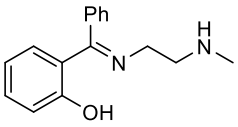
To a solution of 2-hydroxybenzophenone (991 mg, 5.00 mmol) in ethanol (25 mL) was added ethanolamine (0.300 mL, 305 mg, 5.00 mmol) and the resulting solution was refluxed for 16 h. The mixture was concentrated *in vacuo* to yield the title compound (1.21 g, 100%) as a yellow solid which was used without further purification. δ_H (400 MHz, $CDCl_3$) 7.54–7.46 (3H, m, ArH), 7.29–7.19 (3H, m, ArH), 6.95 (1H, dd, *J* = 8.5, 1.0 Hz, ArH), 6.80 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 6.64–6.58 (1H, m, ArH), 3.87 (2H, t, *J* = 5.5 Hz, OCH_2), 3.48 (2H, t, *J* = 5.5 Hz, NCH_2); δ_C (101 MHz, $CDCl_3$) 175.9 (C=N), 164.6 (ArC), 133.5 (ArC), 133.0 (ArC), 131.7 (ArC), 129.2 (ArC), 128.8 (ArC), 127.5 (ArC), 119.4 (ArC), 118.6 (ArC), 117.1 (ArC), 62.2 (OCH_2), 53.4 (NCH_2); ν_{max}/cm^{-1} (thin film) 3351, 3059, 2935, 1605, 1536, 1490, 1443, 1330, 1303, 1257, 1149, 1063, 908, 825, 753, 728, 699, 642; HRMS (ESI); calcd. for $C_{15}H_{16}NO_2^+$, 242.1176. Found: $[MH]^+$, 242.1173 (1.0 ppm error).

2-(Phenyl((2-(phenylamino)ethyl)imino)methyl)phenol (2.93)



To a solution of 2-hydroxybenzophenone (991 mg, 5.00 mmol) in ethanol (25 mL) was added *N*-phenylethylenediamine (0.650 mL, 681 mg, 5.00 mmol) and the resulting solution was refluxed for 4 h. The mixture was concentrated *in vacuo* to yield the title compound (1.58 g, 100%) as a yellow solid which was used without further purification. δ_H (400 MHz, $CDCl_3$) 7.50–7.43 (3H, m, ArH), 7.31 (1H, ddd, *J* = 9.0, 7.5, 2.0 Hz, ArH), 7.19–7.11 (4H, m, ArH), 7.03 (1H, d, *J* = 8.0 Hz, ArH), 6.82 (1H, dd, *J* = 8.0, 2.0 Hz, ArH), 6.75–6.65 (2H, m, ArH), 6.58–6.53 (2H, m, ArH), 3.58 (2H, t, *J* = 6.0 Hz, C=NCH_2), 3.47 (2H, t, *J* = 6.0 Hz, PhNCH_2); δ_C (101 MHz, $CDCl_3$) 175.9 (C=N), 163.3 (ArC), 147.6 (ArC), 133.9 (ArC), 132.7 (ArC), 131.7 (ArC), 129.4 (ArC), 129.1 (ArC), 128.9 (ArC), 127.3 (ArC), 119.9 (ArC), 118.1 (ArC), 117.7 (ArC), 117.6 (ArC), 113.0 (ArC), 50.6 (C=N**C**H_2), 44.4 (PhNCH_2); ν_{max}/cm^{-1} (thin film) 3408, 3053, 2927, 1600, 1573, 1504, 1450, 1330, 1304, 1256, 1111, 910, 825, 749, 692; HRMS (ESI); calcd. for $C_{21}H_{21}N_2O^+$, 317.1648. Found: $[MH]^+$, 317.1652 (–1.1 ppm error).

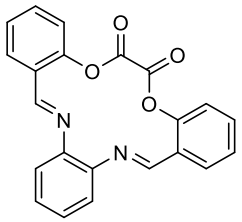
2-(((2-(Methylamino)ethyl)imino)(phenyl)methyl)phenol (2.94)



To a solution of 2-hydroxybenzophenone (991 mg, 5.00 mmol) in ethanol (25 mL) was added *N*-methylethylenediamine (0.440 mL, 371 mg, 5.00 mmol) and the resulting solution was refluxed for 4 h. The mixture was concentrated *in vacuo* to yield the title compound (1.27 g, 100%) as a yellow oil which was used without further purification. δ_H (400 MHz, $CDCl_3$) 7.53–7.43 (3H, m, ArH), 7.29–7.23 (1H, m, ArH), 7.21–7.17 (2H, m, ArH), 6.97 (1H, dd, *J* = 8.5, 1.5 Hz, ArH), 6.80 (1H, dd, *J* = 8.0, 2.0 Hz, ArH), 6.65–6.60 (1H, m, ArH), 3.45 (2H, t, *J* = 6.0 Hz, C=NCH_2), 2.87 (2H, t, *J* = 6.0 Hz, MeNC**H**$_2$), 2.41 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 175.3 (C=N), 163.5 (ArC), 133.8 (ArC), 132.6 (ArC), 131.5 (ArC), 129.1 (ArC), 128.8 (ArC), 127.3 (ArC), 119.7 (ArC), 118.1 (ArC), 117.4 (ArC), 52.1 (MeN**C**H_2), 51.2 (C=N**C**H_2), 36.3 (CH_3); ν_{max}/cm^{-1} (thin film) 3324, 3058, 2933, 1606, 1573, 1493, 1443, 1330, 1301, 1255,

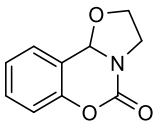
1147, 825, 752, 699, 642; HRMS (ESI); calcd. for $C_{16}H_{19}N_2O^+$, 255.1492. Found: $[MH]^+$, 255.1496 (–1.5 ppm error).

(13*E*,19*E*)-Tribenzo[*e*,*i*,*m*][1,4]dioxa[8,11]diazacyclotetradecine-6,7-dione (2.108)



To a solution of *N*,*N*'-bis(salicylidene)-*o*-phenylenediamine **2.86** (316 mg, 1.00 mmol) and triethylamine (0.700 mL, 506 mg, 5.00 mmol) in DCM (10 mL) was added oxalyl chloride (0.100 mL, 140 mg, 1.10 mmol) and the mixture was stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo* and purified by silica plug filtration (ethyl acetate) to yield the title compound (216 mg, 58%) as a brown solid. δ_H (400 MHz, $CDCl_3$) 8.50 (2H, s, NCH), 7.61 (2H, dd, *J* = 7.5, 1.5 Hz, ArH), 7.47 (2H, td, *J* = 7.5, 1.5 Hz, ArH), 7.36 (2H, td, *J* = 7.5, 1.5 Hz, ArH), 7.28–7.25 (2H, m, ArH), 7.23–7.16 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 155.8 (NCH), 155.1 (CO), 148.2 (ArC), 144.9 (ArC), 133.9 (ArC), 131.8 (ArC), 128.1 (ArC), 127.2 (ArC), 127.0 (ArC), 123.1 (ArC), 117.4 (ArC); v_{max}/cm^{-1} (thin film) 2879, 1789, 1765, 1620, 1572, 1482, 1374, 1279, 1180, 1130, 906, 831, 756, 724, 647; HRMS (ESI); calcd. for $C_{22}H_{15}N_2O_4^+$, 371.1026. Found: $[MH]^+$, 371.1010 (4.4 ppm error).

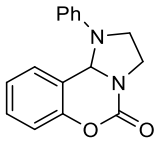
2,3-Dihydro-5*H*,10*bH*-benzo[*e*]oxazolo[3,2-*c*][1,3]oxazin-5-one (2.113)



To a solution of 2-(((2-hydroxyethyl)imino)methyl)phenol **2.88** (165 mg, 1.00 mmol) and triethylamine (0.700 mL, 506 mg, 5.00 mmol) in DCM (10 mL) was added triphosgene (148 mg, 0.500 mmol) and the mixture was stirred at RT for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (25 mL) and extracted with DCM (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 1:1 hexane:ethyl acetate) to yield the title compound (83 mg, 43%) as a yellow oil. R_f 0.45 (1:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.43–7.35 (2H, m, ArH), 7.21 (1H, t, *J* = 7.5 Hz, ArH), 7.10 (1H, d, *J* = 8.0 Hz, ArH), 5.69

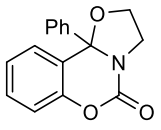
(1H, s, CH), 4.20–3.99 (3H, m, CHH'), 3.64 (1H, ddd, *J* = 10.0, 8.0, 4.0 Hz, C**H**H'); δ_C (101 MHz, $CDCl_3$) 148.7 (CO or ArC), 148.0 (CO or ArC), 131.1 (ArC), 126.5 (ArC), 124.8 (ArC), 116.5 (2 x ArC), 84.3 (CH), 64.0 (CH_2), 45.3 (CH_2); ν_{max}/cm^{-1} 2898, 1722, 1621, 1598, 1462, 1428, 1335, 1204, 1070, 1040, 979, 910, 751, 671; HRMS (ESI); calcd. for $C_{10}H_9NO_3Na^+$, 214.0457. Found: $[MNa]^+$, 214.0481 (–3.1 ppm error).

1-Phenyl-1,2,3,10*b*-tetrahydro-5*H*-benzo[*e*]imidazo[1,2-*c*][1,3]oxazin-5-one (2.123)



To a solution of 2-(((2-(phenylamino)ethyl)imino)methyl)phenol **2.89** (240 mg, 1.00 mmol) and triethylamine (0.700 mL, 506 mg, 5.00 mmol) in DCM (10 mL) was added triphosgene (119 mg, 0.400 mmol) and the mixture was stirred at RT for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 7:3 hexane:ethyl acetate) to yield the title compound (152 mg, 57%) as a white solid. R_f 0.35 (7:3 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.38–7.30 (3H, m, ArH), 7.21–7.15 (2H, m, ArH), 7.12–7.06 (1H, m, ArH), 6.94 (1H, t, *J* = 7.5 Hz, ArH), 6.87–6.80 (2H, m, ArH), 5.96 (1H, s, CH), 4.09–4.01 (1H, m, C**H**H'), 3.82–3.75 (2H, m, C**HH'**), 3.68–3.59 (1H, m, CH**H'**); δ_C (101 MHz, $CDCl_3$) 150.0 (CO or ArC), 149.1 (CO or ArC), 147.3 (CO or ArC), 129.7 (ArC), 129.6 (ArC), 125.0 (ArC), 124.6 (ArC), 123.1 (ArC), 119.6 (ArC), 116.5 (ArC), 114.4 (ArC), 69.6 (CH), 48.4 (CH_2), 43.7 (CH_2); ν_{max}/cm^{-1} (thin film) 3069, 2887, 1738, 1597, 1504, 1486, 1460, 1410, 1363, 1326, 1225, 1207, 1061, 750, 695; HRMS (ESI); calcd. for $C_{16}H_{15}N_2O_2^+$, 267.1128. Found: $[MH]^+$, 267.1134 (–2.3 ppm error).

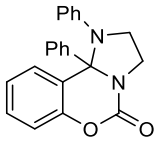
10*b*-Phenyl-2,3-dihydro-5*H*,10*bH*-benzo[*e*]oxazolo[3,2-*c*][1,3]oxazin-5-one (2.127)



To a solution of 2-(((2-hydroxyethyl)imino)(phenyl)methyl)phenol **2.92** (121 mg, 0.500 mmol) and triethylamine (0.350 mL, 253 mg, 2.50 mmol) in DCM (5 mL) was added

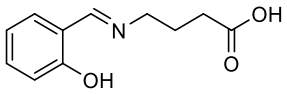
triphosgene (59 mg, 0.200 mmol) and the mixture was stirred at RT for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (120 mg, 90%) as a colourless oil. R_f 0.31 (8:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.52–7.46 (2H, m, ArH), 7.41–7.26 (5H, m, ArH), 7.15–7.09 (2H, m, ArH), 4.24–4.14 (2H, m, 2 x C**H**H'), 4.03–3.95 (1H, m, CH**H'**), 3.51–3.42 (1H, m, CH**H'**); δ_C (101 MHz, $CDCl_3$) 148.4 (CO or ArC), 147.4 (CO or ArC), 141.5 (ArC), 130.2 (ArC), 129.1 (ArC), 128.9 (ArC), 125.9 (ArC), 125.1 (ArC), 124.9 (ArC), 122.4 (ArC), 116.6 (ArC), 93.0 (Ar_2C), 63.3 (CH_2), 44.4 (CH_2); ν_{max}/cm^{-1} (thin film) 2899, 1725, 1596, 1490, 1460, 1383, 1331, 1303, 1218, 1070, 1050, 932, 858, 756, 727, 698, 633, 509; HRMS (ESI); calcd. for $C_{16}H_{14}NO_3^+$, 268.0968. Found: $[MH]^+$, 268.0970 (–0.6 ppm error).

1,10*b*-Diphenyl-1,2,3,10*b*-tetrahydro-5*H*-benzo[*e*]imidazo[1,2-*c*][1,3]oxazin-5-one (2.129)



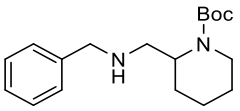
To a solution of 2-(phenyl((2-(phenylamino)ethyl)imino)methyl)phenol **2.93** (158 mg, 0.500 mmol) and triethylamine (0.350 mL, 253 mg, 2.50 mmol) in DCM (5 mL) was added triphosgene (59 mg, 0.200 mmol) and the mixture was stirred at RT for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (62 mg, 36%) as a yellow oil. R_f 0.34 (8:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.63–7.57 (2H, m, ArH), 7.40–7.27 (3H, m, ArH), 7.18–7.08 (4H, m, ArH), 7.00–6.83 (5H, m, ArH), 4.27–4.18 (1H, m, C**H**H'), 3.65–3.50 (3H, m, CH**H'**, C**HH'**); δ_C (101 MHz, $CDCl_3$) 149.1 (CO or ArC), 148.6 (CO or ArC), 147.9 (CO or ArC), 143.1 (ArC), 129.5 (ArC), 129.1 (ArC), 128.9 (ArC), 128.6 (ArC), 127.7 (ArC), 125.9 (ArC), 124.5 (ArC), 124.2 (ArC), 124.1 (ArC), 121.9 (ArC), 116.5 (ArC), 85.0 (Ar_2C), 50.8 (CH_2), 44.1 (CH_2); ν_{max}/cm^{-1} (thin film) 2961, 1717, 1596, 1489, 1457, 1386, 1324, 1214, 1071, 907, 753, 725, 698; HRMS (ESI); calcd. for $C_{22}H_{18}N_2O_2Na^+$, 365.1260. Found: $[MNa]^+$, 365.1269 (–2.2 ppm error).

4-((2-Hydroxybenzylidene)amino)butanoic acid (2.133)



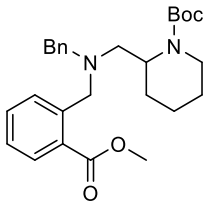
To a solution of salicylaldehyde (0.530 mL, 611 mg, 5.00 mmol) in ethanol (50 mL) was added *γ*-aminobutyric acid (516 mg, 5.00 mmol) and the resulting solution was refluxed for 4 h. The mixture was concentrated *in vacuo* to yield a 1:0.1 mixture of title compound:salicylaldeyde (935 mg, 85%) as a yellow oil which was used without further purification. δ_H (400 MHz, $CDCl_3$) 8.36 (1H, s, CH), 7.32 (1H, td, *J* = 8.0, 1.5 Hz, ArH), 7.27–7.24 (1H, m, ArH), 6.96 (1H, d, *J* = 8.0 Hz, ArH), 6.88 (1H, td, *J* = 8.0, 1.5 Hz, ArH), 3.68 (2H, td, *J* = 7.0, 1.5 Hz, NCH_2), 2.48 (2H, t, *J* = 7.0 Hz, C**H**$_2CO_2H$), 2.07 (2H, p, *J* = 7.0 Hz, CH_2C**H**$_2CH_2$); δ_C (101 MHz, $CDCl_3$) 179.0 (CO), 165.7 (C=N), 161.9 (2 x ArC), 132.7 (ArC), 131.6 (ArC), 118.6 (ArC), 117.4 (ArC), 58.2 (NCH_2), 31.7 (**C**H_2CO_2H), 25.8 (CH_2**C**H_2CH_2); v_{max}/cm^{-1} (thin film) 3202, 2934, 1710, 1631, 1496, 1399, 1277, 1194, 1149, 1089, 1018, 849, 754; HRMS (ESI); calcd. for $C_{11}H_{14}NO_3^+$, 208.0968. Found: $[MH]^+$, 208.0971 (–1.4 ppm error).

***tert*-Butyl 2-((benzylamino)methyl)piperidine-1-carboxylate (2.141)**



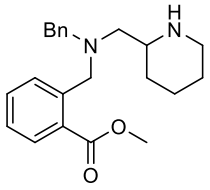
To a solution of *tert*-butyl 2-(aminomethyl)piperidine-1-carboxylate (1.00 mL, 1.01 g, 4.71 mmol) in methanol (25 mL) was added benzaldehyde (0.570 mL, 595 mg, 5.60 mmol) and the resulting solution was stirred at RT for 6 h. Sodium borohydride (533 mg, 14.1 mmol) was added in portions and then stirred at RT for 30 mins. The reaction mixture was concentrated *in vacuo*. Water (25 mL) was added and the product was extracted with DCM (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 13:6:1 hexane:ethyl acetate:triethylamine) to yield the title compound (1.15 g, 80%) as a yellow oil. R_f 0.52 (13:6:1 hexane:ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.37–7.21 (5H, m, ArH), 4.42–4.31 (1H, m, NCH), 4.02–3.92 (1H, m, NC**H**H'), 3.85 (1H, d, *J* = 13.5 Hz, PhC**H**H'), 3.78 (1H, d, *J* = 13.5 Hz, PhCH**H'**), 2.90 (1H, dd, *J* = 12.0, 8.5 Hz, NC**H**H'), 2.74–2.60 (2H, m, 2 x NCH**H'**), 1.71–1.36 (15H, m, $C(CH_3)_3$, CHH'). Characterisation data matched those reported in the literature.[121]

tert-Butyl 2-((benzyl(2-(methoxycarbonyl)benzyl)amino)methyl)piperidine-1-carboxylate (2.143)



tert-Butyl 2-((benzylamino)methyl)piperidine-1-carboxylate **2.141** (687 mg, 2.26 mmol) was dissolved in DCM (4.6 mL) and to this was added methyl 2-(bromomethyl)benzoate (641 mg, 2.80 mmol) and potassium carbonate (567 mg, 4.10 mmol). The resulting mixture was stirred at RT for 22 h. The reaction mixture was diluted with DCM (20 mL), washed with water (25 mL) and brine (2 x 25 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 9:1 hexane:ethyl acetate) to yield the title compound (770 mg, 74%) as a yellow oil. R_f 0.29 (9:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.80–7.72 (2H, m, ArH), 7.46 (1H, t, *J* = 7.5 Hz, ArH), 7.36–7.19 (6H, m, ArH), 4.59–4.26 (1H, m, CHH'), 4.17–4.05 (1H, m, CHH'), 3.96–3.77 (5H, m, OCH_3, CHH'), 3.71–3.36 (2H, m, CHH'), 2.67–2.29 (3H, m, CH, CHH'), 1.79–1.18 (14H, m, $C(CH_3)_3$, CHH'), 0.94–0.79 (1H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 168.5 (**C**O_2Me), 155.0 (NCO_2), 141.2 (ArC), 139.3 (ArC), 131.5 (ArC), 130.8 (ArC), 130.3 (ArC), 129.9 (ArC), 129.2 (ArC), 128.1 (ArC), 126.9 (ArC), 126.6 (ArC), 79.2 (**C**$(CH_3)_3$), 58.7 (Ar**C**H_2), 56.3 (Ar**C**H_2), 52.6 (NCH_2), 52.0 (OCH_3), 39.3 (CH), 29.7 (CH_2), 28.6 ($C(\mathbf{C}H_3)_3$), 26.2 (CH_2), 25.3 (CH_2), 18.7 (CH_2); ν_{max}/cm^{-1} (thin film) 2932, 1723, 1686, 1450, 1415, 1364, 1267, 1172, 1148, 1076, 1045, 741, 700; HRMS (ESI); calcd. for $C_{27}H_{37}N_2O_4^+$, 453.2784. Found: $[MH]^+$, 453.2745 (0.5 ppm error).

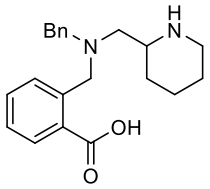
Methyl 2-((benzyl(piperidin-2-ylmethyl)amino)methyl)benzoate (2.144)



tert-Butyl 2-((benzyl(2-(methoxycarbonyl)benzyl)amino)methyl)piperidine-1-carboxylate **2.143** (870 mg, 1.92 mmol) was dissolved in 1,4-dioxane (7.3 mL) and methanol (7.3 mL).

To this was added HCl (7.30 mL, 4 M in dioxane, 29.2 mmol) and the reaction was stirred at RT for 18 h. The solution was diluted with ethyl acetate (100 mL) and neutralised using 2 M aq. NaOH. The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 19:1 ethyl acetate:triethylamine) to yield the title compound (616 mg, 92%) as a yellow oil. R_f 0.45 (19:1 ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.76 (1H, dd, *J* = 7.5, 1.5 Hz, ArH), 7.64 (1H, d, *J* = 8.0 Hz, ArH), 7.46 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 7.31–7.19 (6H, m, ArH), 4.06 (1H, d, *J* = 14.5 Hz, ArC**H**H'), 3.89 (3H, s, CH_3), 3.83 (1H, d, *J* = 14.5 Hz, ArCH**H'**), 3.62 (1H, d, *J* = 13.5 Hz, PhC**H**H'), 3.48 (1H, d, *J* = 13.5 Hz, PhCH**H'**), 2.99–2.93 (1H, m, HNC**H**H'), 2.54–2.28 (5H, m, HNCH**H'**, NC**H**H'CH, NCH**H'**CH, CH, NH), 1.74–1.66 (1H, m, CHH'), 1.55–1.48 (2H, m, CHH'), 1.45–1.34 (1H, m, CHH'), 1.25–1.16 (1H, m, CHH'), 1.00–0.88 (1H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 168.7 (**C**O_2Me), 141.0 (ArC), 139.1 (ArC), 131.5 (ArC), 130.9 (ArC), 130.2 (ArC), 130.0 (ArC), 129.0 (ArC), 128.2 (ArC), 127.0 (ArC), 126.8 (ArC), 61.6 (N**C**H_2CH), 59.9 (Ph**C**H_2), 57.3 (Ar**C**H_2), 54.6 (CH), 52.0 (CH_3), 46.8 (HNCH_2), 30.8 (CH_2), 26.3 (CH_2), 24.8 (CH_2); ν_{max}/cm^{-1} (thin film) 2929, 2799, 1721, 1601, 1494, 1434, 1265, 1125, 1080, 967, 739, 698; HRMS (ESI): calcd. for $C_{22}H_{29}N_2O_2^+$, 353.2224. Found: $[MH]^+$, 353.2222 (0.4 ppm error).

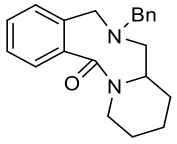
2-((Benzyl(piperidin-2-ylmethyl)amino)methyl)benzoic acid (2.145)



To a solution of methyl 2-((benzyl(piperidin-2-ylmethyl)amino)methyl)benzoate **2.144** (78 mg, 0.220 mmol) in THF (0.44 mL) was added lithium hydroxide (0.480 mL, 0.5 M in water, 0.240 mmol) and the mixture was heated to reflux for 22 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 15:4:1 ethyl acetate:methanol:triethylamine) to yield the title compound (67 mg, 90%) as a white solid. R_f 0.25 (15:4:1 ethyl acetate:methanol:triethylamine); m.p. 147–152 °C; δ_H (400 MHz, $CDCl_3$) 7.64 (1H, dd, *J* = 7.0, 2.0 Hz, ArH), 7.31–7.12 (8H, m, ArH), 4.32 (1H, d, *J* = 12.5 Hz, ArCHH'), 3.67 (1H, d, *J* = 14.0 Hz, ArCHH'), 3.59–3.32 (3H, m, 2 x ArCHH', CHH'), 3.22–3.01 (3H, m, CHH', CH), 2.73 (1H, t, *J* = 12.0 Hz, CHH'), 2.40–2.32 (1H, m, CHH'), 1.86–1.53 (5H,

m, CHH', NH), 1.40–1.30 (1H, m, CHH'); δ_C (400 MHz, $CDCl_3$) 176.9 (CO_2H), 139.4 (ArC), 136.3 (ArC), 135.1 (ArC), 130.7 (ArC), 129.9 (ArC), 128.8 (ArC), 128.4 (ArC), 128.2 (ArC), 127.7 (ArC), 127.2 (ArC), 58.2 ($ArCH_2$), 56.7 ($ArCH_2$), 53.6 (CH), 45.7 (CH_2), 43.4 (CH_2), 26.6 (CH_2), 22.4 (CH_2), 22.1 (CH_2); v_{max}/cm^{-1} (thin film) 3397, 2942, 2811, 1619, 1582, 1549, 1447, 1390, 909, 750, 729, 661; HRMS (ESI); calcd. for $C_{21}H_{27}N_2O_2^+$, 339.2067. Found: $[MH]^+$, 339.2063 (1.2 ppm error).

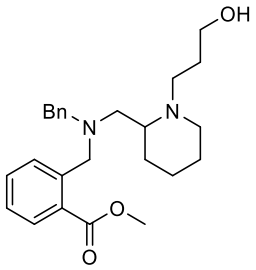
6-Benzyl-5,6,7,7*a*,8,9,10,11-octahydro-13*H*-benzo[*f*]pyrido[1,2-*a*][1,4]diazocin-13-one (2.146)



A round-bottom flask was charged with 2-((benzyl(piperidin-2-ylmethyl)amino)methyl)benzoic acid **2.145** (65 mg, 0.192 mmol) and DMF (1.9 mL). To this was added DIPEA (0.170 mL, 129 mg, 1.00 mmol), EDC·HCl (58 mg, 0.303 mmol) and HOBt (41 mg, 0.303 mmol). The resulting mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (20 mL) and then washed with brine (3 x 20 mL). The combined aqueous layers were then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were then dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 15:4:1 hexane:ethyl acetate:triethylamine) to yield the title compound (50 mg, 82%) as a colourless oil. R_f 0.38 (15:4:1 hexane:ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.43–7.30 (5H, m, ArH), 7.28–7.21 (3H, m, ArH), 6.99–6.94 (1H, m, ArH), 4.47 (1H, d, *J* = 13.5 Hz, C**H**H'NCO), 4.01 (1H, d, *J* = 16.5 Hz, Ar^1C**H**H'), 3.94–3.88 (1H, m, NCH), 3.84 (1H, d, *J* = 13.5 Hz, Ar^2C**H**H'), 3.73 (1H, d, *J* = 13.5 Hz, Ar^2CH**H'**), 3.64 (1H, d, *J* = 16.5 Hz, Ar^1CH**H'**), 3.13 (1H, td, *J* = 12.0, 1.5 Hz, NC**H**H'CH), 2.57 (1H, td, *J* = 13.5, 3.5 Hz, CH**H'**NCO), 2.32 (1H, dd, *J* = 12.0, 3.5 Hz, NCH**H'**CH), 1.75–1.68 (1H, m, CHH'), 1.65–1.52 (2H, m, CHH'), 1.49–1.29 (3H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 173.5 (CO), 138.7 (ArC), 138.1 (ArC), 135.0 (ArC), 129.1 (2 x ArC), 128.8 (ArC), 128.5 (ArC), 127.4 (ArC), 127.0 (ArC), 126.8 (ArC), 63.3 ($ArCH_2$), 59.1 ($ArCH_2$), 57.0 (N**C**H_2CH), 51.5 (CH), 37.8 (**C**H_2NCO), 27.3 (CH_2), 24.5 (CH_2), 19.1 (CH_2); v_{max}/cm^{-1} (thin film) 2925, 2853, 1624, 1450, 1408, 1370, 1323, 1278, 1132, 1098, 1018,

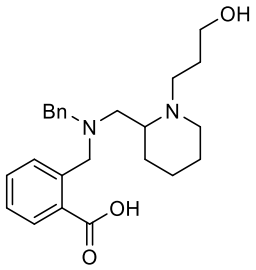
909, 730, 699, 646; HRMS (ESI); calcd. for $C_{21}H_{25}N_2O^+$, 321.1961. Found: $[MH]^+$, 321.1960 (0.6 ppm error).

Methyl 2-((benzyl((1-(3-hydroxypropyl)piperidin-2-yl)methyl)amino)methyl)benzoate (2.147)



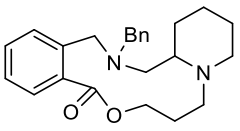
Methyl 2-((benzyl(piperidin-2-ylmethyl)amino)methyl)benzoate **2.144** (255 mg, 0.723 mmol) was dissolved in acetonitrile (1.4 mL) and to this was added potassium carbonate (100 mg, 0.724 mmol) and 3-bromo-1-propanol (0.070 mL, 100 mg, 0.719 mmol). The reaction mixture was heated to reflux for 20 h. The solid material was filtered off, washed with ethyl acetate and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 19:1 diethyl ether:triethylamine) to yield the title compound (222 mg, 75%) as a colourless oil. R_f 0.33 (19:1 diethyl ether:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.76 (1H, d, *J* = 7.5 Hz, ArH), 7.70 (1H, d, *J* = 8.0 Hz, ArH), 7.46 (1H, t, *J* = 7.5 Hz, ArH), 7.31–7.17 (6H, m, ArH), 3.95–3.81 (5H, m, $ArCH_2$, CH_3), 3.64–3.61 (4H, m, $ArCH_2$, C**HH'**), 2.96–2.86 (1H, m, CHH'), 2.75–2.59 (2H, m, CHH'), 2.53–2.45 (1H, m, NCH), 2.42–2.31 (2H, m, CHH'), 2.16–2.08 (1H, m, CHH'), 1.73–1.57 (2H, m, CHH'), 1.48–1.13 (6H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 168.3 (CO), 140.8 (ArC), 138.9 (ArC), 131.4 (ArC), 130.8 (ArC), 130.4 (ArC), 129.9 (ArC), 129.3 (ArC), 128.1 (ArC), 127.0 (ArC), 126.7 (ArC), 64.1 (CH_2), 59.8 ($ArCH_2$), 58.5 (NCH), 57.2 ($ArCH_2$), 55.1 (CH_2), 54.1 (CH_2), 51.9 (CH_3), 50.4 (CH_2), 30.3 (CH_2), 27.3 (CH_2), 24.9 (CH_2), 21.9 (CH_2); ν_{max}/cm^{-1} (thin film) 3397, 2928, 2852, 1721, 1450, 1433, 1363, 1266, 1128, 1079, 1046, 967, 913, 740, 700; HRMS (ESI); calcd. for $C_{25}H_{35}N_2O_3^+$, 411.2642. Found: $[MH]^+$, 411.2642 (0.1 ppm error).

2-((Benzyl((1-(3-hydroxypropyl)piperidin-2-yl)methyl)amino)methyl)benzoic acid (2.136)



To a solution of methyl 2-((benzyl((1-(3-hydroxypropyl)piperidin-2-yl)methyl)amino)methyl)benzoate **2.147** (220 mg, 0.536 mmol) in THF (1.1 mL) was added lithium hydroxide (1.72 mL, 0.5 M in water, 0.860 mmol) and the mixture was refluxed for 22 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 15:4:1 ethyl acetate:methanol:triethylamine) to yield the title compound (140 mg, 65%) as a white solid. R_f 0.28 (15:4:1 ethyl acetate:methanol:triethylamine); m.p. 51–55 °C; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* = 7.5 Hz, ArH), 7.23–7.05 (8H, m, ArH), 4.82 (1H, d, *J* = 12.0 Hz, ArC**H**H'), 3.76–3.46 (5H, m, NCH, ArCH**H'**), 2.99–2.89 (1H, m, CHH'), 2.86 (1H, d, *J* = 11.0 Hz, CHH'), 2.73 (1H, d, *J* = 12.5 Hz, CHH'), 2.63 (1H, t, *J* = 13.0 Hz), 2.50–2.36 (2H, m, CHH'), 1.96 (1H, d, *J* = 14.0 Hz, CHH'), 1.81–1.59 (2H, m, CHH'), 1.52–1.20 (6H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 176.7 (CO), 139.9 (ArC), 137.3 (ArC), 135.3 (ArC), 130.5 (ArC), 130.3 (ArC), 129.0 (ArC), 128.1 (ArC), 127.9 (ArC), 127.6 (ArC), 127.3 (ArC), 58.9 (2 x CH_2), 58.3 (NCH), 57.9 (CH_2), 54.0 (CH_2), 47.7 (CH_2), 40.3 (CH_2), 26.9 (CH_2), 22.4 (CH_2), 21.8 (CH_2), 17.9 (CH_2); v_{max}/cm^{-1} (thin film) 3247, 2941, 1584, 1562, 1440, 1371, 1065, 922, 753, 726, 703; HRMS (ESI); calcd. for $C_{24}H_{33}N_2O_3^+$, 397.2486. Found $[MH]^+$, 397.2484 (0.3 ppm error).

16-Benzyl-1,2,3,4,7,8,15,16,17,17*a*-decahydro-6*H*,10*H*-benzo[*j*]pyrido[1,2-*e*][1]oxa[5,8]diazacyclododecin-10-one (2.139)



Method A

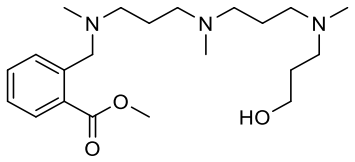
To a solution of 2-((benzyl((1-(3-hydroxypropyl)piperidin-2-yl)methyl)amino)methyl)benzoic acid **2.136** (70 mg, 0.178 mmol) in chloroform (1.8 mL)

was added DIPEA (0.090 mL, 70 mg, 0.542 mmol) followed by T3P (0.180 mL, 50% in ethyl acetate, 0.310 mmol) and the mixture was stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 19:1 ethyl acetate:triethylamine) to yield the title compound (12 mg, 18%) as a colourless oil. Characterisation data is given below.

Method B

A round-bottom flask was charged with 2-((benzyl((1-(3-hydroxypropyl)piperidin-2-yl)methyl)amino)methyl)benzoic acid **2.136** (66 mg, 0.166 mmol) and DMF (1.7 mL). To this was added DIPEA (0.160 mL, 119 mg, 0.921 mmol), EDC·HCl (52 mg, 0.271 mmol) and HOBt (36 mg, 0.266 mmol). The resulting mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (20 mL) and then washed with brine (3 x 20 mL). The combined aqueous layers were then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were then dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 15:4:1 ethyl acetate:hexane:triethylamine) to yield the title compound (38 mg, 59%) as a colourless oil. R_f 0.50 (15:4:1 ethyl acetate:hexane:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.62 (1H, dd, *J* = 7.5, 1.5 Hz, ArH), 7.40–7.30 (2H, m, ArH), 7.26–7.15 (6H, m, ArH), 4.89 (1H, dt, *J* = 11.0, 3.5 Hz, OC**H**H'), 4.23 (1H, d, *J* = 12.5 Hz, ArC**H**H'), 3.93 (1H, t, *J* = 11.0 Hz, OCH**H'**), 3.58 (1H, d, *J* = 12.5 Hz, ArCH**H'**), 3.44 (1H, d, *J* = 12.5 Hz, PhC**H**H'), 3.19 (1H, ddd, *J* = 14.0, 11.0, 3.0 Hz, NC**H**H'C_2H_4O), 3.00 (1H, d, *J* = 12.5 Hz, PhCH**H'**), 2.94–2.84 (1H, m, NCH**H'**C_2H_4O), 2.73 (1H, dd, *J* = 14.5, 7.0 Hz, NC**H**H'CH), 2.68–2.62 (1H, m, NC**H**H'), 2.29–2.15 (3H, m, NCH**H'**CH, NCH**H'**, CHH'), 2.05–1.97 (1H, m, NCH), 1.72–1.61 (1H, m, CHH'), 1.54–1.44 (2H, m, CHH'), 1.40–1.22 (2H, m, CHH'), 1.02–0.81 (2H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 170.4 (CO), 138.2 (ArC), 137.3 (ArC), 133.6 (ArC), 131.2 (ArC), 130.6 (ArC), 130.2 (ArC), 129.9 (ArC), 128.0 (ArC), 127.7 (ArC), 127.1 (ArC), 64.0 (N**C**H_2CH), 63.5 (OCH_2), 61.9 ($ArCH_2$), 59.7 ($PhCH_2$), 56.9 (NCH), 52.0 (NCH_2), 50.2 (N**C**$H_2C_2H_4O$), 31.8 (CH_2), 25.7 (CH_2), 24.3 (CH_2), 22.4 (CH_2); v_{max}/cm^{-1} (thin film) 2929, 2792, 1715, 1451, 1380, 1288, 1124, 1090, 1047, 907, 729, 700; HRMS (ESI); calcd. for $C_{24}H_{31}N_2O_2^+$, 379.2380. Found $[MH]^+$, 379.2375 (1.3 ppm error).

Methyl 2-(((3-((3-((3-hydroxypropyl)(methyl)amino)propyl)(methyl)amino)propyl)(methyl)amino)methyl)benzoate (2.158)

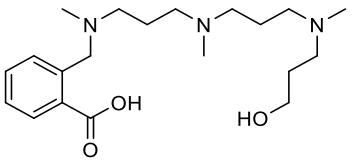


To a solution of methyl 2-(bromomethyl)benzoate (229 mg, 1.00 mmol) in DCM (2.0 mL) was added potassium carbonate (346 mg, 2.50 mmol) and *N*,*N*-bis[3-(methylamino)propyl]methylamine (0.400 mL, 347 mg, 2.00 mmol) and the reaction mixture was stirred at RT for 18 h. Water (20 mL) was added and the product extracted with DCM (3 x 20 mL). the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 10:9:1 methanol:DCM:triethylamine) to yield methyl 2-((methyl(3-(methyl(3-(methylamino)propyl)amino)propyl)amino)methyl)benzoate **2.157** (158 mg) with minor impurities as a yellow oil which was used without further purification.

To a solution of methyl 2-((methyl(3-(methyl(3-(methylamino)propyl)amino)propyl)amino)methyl)benzoate **2.157** (158 mg) in DCM (4.6 mL) was added potassium carbonate (115 mg, 0.833 mmol) and 3-bromo-1-propanol (0.050 mL, 77 mg, 0.556 mmol) and the reaction mixture was stirred at RT for 18 h. The solids were filtered off and washed with DCM and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2 19:1 methanol:triethylamine) to yield the title compound (97 mg, 26% over 2-steps) as a yellow oil. R_f 0.49 (19:1 methanol:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.67 (1H, d, *J* = 7.5 Hz, ArH), 7.42–7.35 (2H, m, ArH), 7.27–7.21 (1H, m, ArH), 3.82 (3H, s, OCH_3), 3.73–3.68 (4H, m, $ArCH_2$, OCH_2), 2.59 (2H, t, *J* = 6.0 Hz, NCH_2), 2.49–2.39 (6H, m, 3 x NCH_2), 2.35 (2H, t, *J* = 7.0 Hz, NCH_2), 2.26 (3H, s, NCH_3), 2.24 (3H, s, NCH_3), 2.14 (3H, s, NCH_3), 1.76–1.60 (6H, m, 3 x CH_2); δ_C (101 MHz, $CDCl_3$) 169.0 (CO), 140.0 (ArC), 131.3 (ArC), 131.1 (ArC), 130.2 (ArC), 129.9 (ArC), 127.0 (ArC), 63.3 (OCH_2), 60.3 ($ArCH_2$), 57.4 (NCH_2), 55.8 (NCH_2), 55.4 (NCH_2), 55.3 (2 x NCH_2), 52.0 (OCH_3), 42.1 (NCH_3), 41.8 (NCH_3), 41.6 (NCH_3), 27.8 (CH_2), 24.0 (CH_2), 23.7 (CH_2); ν_{max}/cm^{-1} (thin film) 3364, 2947, 2841, 2792, 1721, 1455, 1433, 1366, 1269, 1248, 1122,

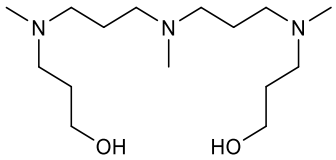
1081, 1046, 963, 739; HRMS (ESI); calcd. for $C_{21}H_{38}N_3O_3^+$, 380.2908. Found: $[MH]^+$, 380.2920 (–3.3. ppm error).

2-(((3-((3-((3-Hydroxypropyl)(methyl)amino)propyl)(methyl)amino)propyl)(methyl)amino)methyl)benzoic acid (2.159)



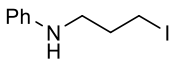
To a solution of methyl 2-(((3-((3-((3-hydroxypropyl)(methyl)amino)propyl)(methyl)amino)propyl)(methyl)amino)methyl)benzoate **2.158** (97 mg, 0.256 mmol) in THF (0.51 mL) was added lithium hydroxide (0.560 mL, 0.5 M in water, 0.282 mmol) and the reaction mixture was heated to reflux for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 19:1 methanol:triethylamine) to yield the title compound (92 mg, 98%) as a colourless oil. R_f 0.32 (19:1 methanol:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.97–7.92 (1H, m, ArH), 7.35–7.27 (2H, m, ArH), 7.25–7.20 (1H, m, ArH), 4.07 (2H, s, $ArCH_2$), 3.65 (2H, t, *J* = 5.5 Hz, OCH_2), 2.92 (2H, t, *J* = 7.5 Hz, NCH_2), 2.72 (2H, t, *J* = 6.5 Hz, NCH_2), 2.57–2.48 (5H, m, NCH_2, NCH_3), 2.36–2.22 (7H, m, 2 x NCH_2, NCH_3), 2.07 (3H, s, NCH_3), 1.82–1.57 (6H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 172.5 (CO_2H), 138.0 (ArC), 132.2 (ArC), 131.7 (ArC), 130.7 (ArC), 130.5 (ArC), 129.4 (ArC), 62.2 (OCH_2), 60.7 ($ArCH_2$), 56.5 (NCH_2), 55.3 (NCH_2), 54.9 (NCH_2), 54.5 (NCH_2), 53.3 (NCH_2), 41.7 (NCH_3), 41.3 (NCH_3), 39.2 (NCH_3), 27.6 (CH_2), 23.7 (CH_2), 22.4 (CH_2); v_{max}/cm^{-1} (thin film) 3352, 2951, 1299, 1609, 1592, 1567, 1460, 1376, 1296, 1205, 1143, 1058, 908, 724, 641; HRMS (ESI); calcd. for $C_{20}H_{36}N_3O_3^+$, 366.2751. Found: $[MH]^+$, 366.2765 (–3.7 ppm error).

3,3'-(((Methylazanediyl)bis(propane-3,1-diyl))bis(methylazanediyl))bis(propan-1-ol) (2.161)



To a solution of *N*,*N*-bis[3-(methylamino)propyl]methylamine (0.200 mL, 173 mg, 1.00 mmol) in DCM (5 mL) was added potassium carbonate (415 mg, 3.00 mmol) followed by 3-bromo-1-propanol (0.200 mL, 306 mg, 2.20 mmol) and the reaction mixture was stirred at room temperature for 18 h. The solids were filtered off and washed with DCM and the filtrate concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 19:1 methanol:triethylamine) to yield the title compound (165 mg, 57%) as a colourless oil. R_f 0.23 (19:1 MeOH:triethylamine); δ_H (400 MHz, $CDCl_3$) 5.35 (2H, s, OH), 3.64 (4H, t, *J* = 5.5 Hz, C**H**$_2$OH), 2.47 (4H, t, *J* = 6.0 Hz, NCH_2), 2.32–2.21 (8H, m, NCH_2), 2.14 (6H, s, NCH_3), 2.10 (3H, s, NCH_3), 1.62–1.50 (8H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 63.7 (CH_2OH), 57.6 (NCH_2), 56.0 (NCH_2), 55.4 (NCH_2), 42.0 (NCH_3), 41.9 (NCH_3), 27.9 (CH_2), 24.7 (CH_2); ν_{max}/cm^{-1} (thin film) 3329, 2945, 2842, 2791, 1461, 1372, 1318, 1213, 1163, 1057, 923, 831, 730; HRMS (ESI); calcd. for $C_{15}H_{36}N_3O_2^+$, 290.2802: Found $[MH]^+$, 290.2810 (–2.9 ppm error).

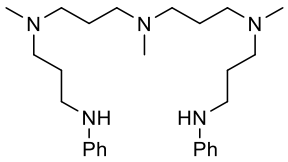
***N*-(3-Iodopropyl)aniline (2.162)**



A solution of imidazole (613 mg, 9.00 mmol) and triphenylphosphine (2.36 g, 9.00 mmol) in DCM (45 mL) was cooled to 0 °C before adding iodine (2.28 g, 9.00 mmol) in portions. Upon complete addition the mixture was warmed to RT and a solution of 3-anilino-1-propanol (1.00 mL, 1.13 g, 7.50 mmol) in DCM (8 mL) was added and the resulting mixture was stirred at RT for 4 h. The reaction mixture was filtered through Celite and the filtrate washed with 5% aq. sodium thiosulfate (2 x 20 mL). The combined aquatic layers were extracted with DCM (40 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (4:1 hexane:ethyl acetate) to yield the title compound (1.81 g, 92%) as an orange oil. R_f 0.62 (4:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.25–7.20 (2H, m, ArH),

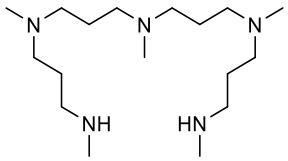
6.80–6.75 (1H, m, ArH), 6.71–6.67 (2H, m, ArH), 4.16 (1H, br s, NH), 3.33–3.27 (4H, m, NCH_2, CH_2I), 2.14 (2H, tt, *J* = 6.5, 6.5 Hz, $NCH_2C\mathbf{H}_2$); δ_C (101 MHz, $CDCl_3$) 147.4 (ArC), 129.5 (ArC), 118.1 (ArC), 113.3 (ArC), 44.4 (NCH_2), 32.5 ($NCH_2\mathbf{C}H_2$), 3.9 (CH_2I); ν_{max}/cm^{-1} (thin film) 3403, 3049, 3019, 2929, 1600, 1504, 1426, 1319, 1256, 1229, 1176, 1072, 990, 869, 746, 691, 507; HRMS (ESI); calcd. for $C_9H_{13}IN^+$, 262.0087. Found: $[MH]^+$, 262.0083 (1.5 ppm error).

N^1,N^3-Dimethyl-N^1-(3-(methyl(3-(phenylamino)propyl)amino)propyl)-N^3-(3-(phenylamino)propyl)propane-1,3-diamine (2.163)



To a solution of *N*-(3-iodopropyl)aniline (1.72 g, 6.59 mmol) in DCM (6 mL) was added potassium carbonate (1.24 g, 9.00 mmol) and *N*,*N*-bis[3-(methylamino)propyl]methylamine (0.600 mL, 520 mg, 3.00 mmol) and the reaction mixture was stirred at RT for 18 h. The solids were filtered off and washed with DCM and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 19:1 MeOH:triethylamine) to yield the title compound (808 mg, 61%) as a yellow oil. R_f 0.34 (19:1 MeOH:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.20–7.14 (4H, m, ArH), 6.68 (2H, t, *J* = 7.0 Hz, ArH), 6.60 (4H, d, *J* = 7.0 Hz, ArH), 3.17 (4H, t, *J* = 6.5 Hz, $PhNCH_2$), 2.47 (4H, t, *J* = 6.5 Hz, NCH_2), 2.39–2.33 (8H, m, NCH_2), 2.24 (6H, s, NCH_3), 2.22 (3H, s, NCH_3), 1.78 (4H, tt, *J* = 6.5, 6.5 Hz, $PhNCH_2C\mathbf{H}_2$), 1.71–1.62 (4H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 148.8 (ArC), 129.3 (ArC), 117.0 (ArC), 112.8 (ArC), 56.6 (NCH_2), 56.1 (NCH_2), 56.0 (NCH_2), 43.4 ($PhNCH_2$), 42.3 (NCH_3), 42.2 (NCH_3), 26.5 ($PhNCH_2\mathbf{C}H_2$), 25.3 (CH_2); ν_{max}/cm^{-1} (thin film) 3292, 2945, 2791, 1602, 1506, 1462, 1319, 1259, 1177, 1073, 991, 865, 746, 692, 509; HRMS (ESI); calcd. for $C_{27}H_{46}N_5^+$, 440.3748. Found: $[MH]^+$, 440.3750 (–0.5 ppm error).

***N*-Methyl-*N*-[3-(methylamino)propyl]-*N*-3-[methyl(3-methyl[3-(methylamino)propyl]aminopropyl)amino]propylamine [penta(1-methylazetane)] (2.167)**

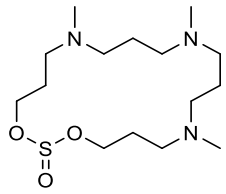


To a solution of *N*,*N*-bis[3-(methylamino)propyl]methylamine (6.00 mL, 5.20 g, 30.0 mmol) in ethanol (30 mL) was added methyl acrylate (6.20 mL, 5.94 g, 69.0 mmol) and the mixture was heated to reflux for 18 h. The reaction mixture was concentrated *in vacuo* to yield methyl 6,10,14-trimethyl-3-oxo-2-oxa-6,10,14-triazaheptadecan-17-oate **2.165** (10.4 g, 100%) as a yellow oil which was used directly in the next step without further purification.

The crude methyl 6,10,14-trimethyl-3-oxo-2-oxa-6,10,14-triazaheptadecan-17-oate **2.165** (10.4 g, 30.0 mmol) was dissolved in ethanol (5 mL) and to this was added methylamine (28.4 mL, 33% in EtOH, 231 mmol) and the reaction mixture was stirred at RT for 5 days. The reaction mixture was concentrated *in vacuo* to yield *N*-6,10,14-tetramethyl-3-oxo-2,6,10,14-tetraazaheptadecan-17-amide **2.166** (10.3 g, 100%) as a yellow oil which was used directly in the next step without further purification.

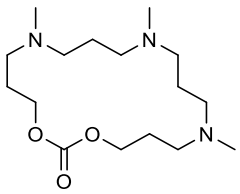
The crude *N*-6,10,14-tetramethyl-3-oxo-2,6,10,14-tetraazaheptadecan-17-amide **2.166** (9.35 g, 27.2 mmol) was dissolved in THF (136 mL) and to this was slowly added lithium aluminium hydride (100 mL, 1 M in THF, 100 mmol). Upon complete addition the reaction mixture was heated to reflux for 18 h. The reaction mixture was cooled to 0 °C and quenched with water (7 mL), potassium hydroxide (8.2 g in 8.2 mL of water) and water (16 mL). The solids were filtered off and washed with DCM and the filtrate was concentrated *in vacuo.* The crude product was purified by Kugelrohr vacuum distillation (185 °C) to yield the title compound (5.66 g, 60%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 2.66–2.55 (4H, m, 2 x NCH_2), 2.46–2.30 (18H, m, 6 x NCH_2, 2 x NCH_3), 2.23–2.18 (9H, m, 3 x NCH_3), 1.71–1.57 (8H, m, 4 x CH_2). Characterisation data matched those reported in the literature.[93]

7,11,15-Trimethyl-1,3-dioxa-2-thia-7,11,15-triazacyclooctadecane 2-oxide (2.173)



To a solution of 3,3'-(((methylazanediyl)bis(propane-3,1-diyl))bis(methylazanediyl))bis(propan-1-ol) **2.161** (165 mg, 0.570 mmol) and DMAP (348 mg, 2.85 mmol) in DCM (5.7 mL) was added thionyl chloride (0.050 mL, 81 mg, 0.684 mmol) and the reaction mixture was stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 19:1 methanol:triethylamine) to yield the title compound (122 mg, 64%) as a yellow oil. R_f 0.38 (19:1 methanol:triethylamine); δ_H (400 MHz, $CDCl_3$) 4.12–3.96 (4H, m, OCH_2), 2.41–2.28 (12H, m, 3 x NCH_2), 2.20 (3H, m, NCH_3), 2.13 (6H, s, NCH_3), 1.82–1.73 (4H, m, CH_2), 1.63–1.54 (4H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 60.6 (OCH_2), 55.6 (NCH_2), 54.8 (NCH_2), 52.7 (NCH_2), 43.0 (NCH_3), 42.5 (NCH_3), 27.4 (CH_2), 24.9 (CH_2); v_{max}/cm^{-1} (thin film) 2947, 2840, 2789, 1647, 1461, 1276, 1317, 1205, 1079, 912, 843, 785, 705; HRMS (ESI); calcd. for $C_{15}H_{34}N_3O_3S^+$, 336. 2315. Found: $[MH]^+$, 336.2324 (–2.6 ppm error).

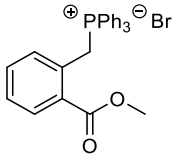
7,11,15-Trimethyl-1,3-dioxa-7,11,15-triazacyclooctadecan-2-one (2.174)



To a solution of 3,3'-(((methylazanediyl)bis(propane-3,1-diyl))bis(methylazanediyl))bis(propan-1-ol) **2.161** (227 mg, 0.784 mmol) and triethylamine (0.550 mL, 397 mg, 3.92 mmol) in DCM (7.8 mL) was added triphosgene (93 mg, 0.314 mmol) and the reaction mixture was stirred at RT for 18h. The reaction mixture was quenched with 7N ammonia in MeOH (0.5 mL) and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 19:1 methanol:triethylamine) to yield the title compound (35 mg, 14%) as a colourless oil. R_f 0.40 (19:1 methanol:triethylamine); δ_H (400 MHz, $CDCl_3$) 4.20 (4H, t, J = 6.0 Hz, 2 x OCH_2), 2.43–2.30

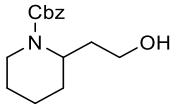
(12H, m, 6 x NCH_2), 2.21 (3H, s, NCH_3), 2.15 (6H, s, 2 x NCH_3), 1.77 (4H, tt, *J* = 6.0, 6.0 Hz, 2 x $OCH_2C\mathbf{H}_2$), 1.60 (4H, tt, *J* = 7.0 Hz, 2 x CH_2); δ_C (101 MHz, $CDCl_3$) 155.3 (CO), 65.7 (OCH_2), 56.2 (NCH_2), 55.6 (NCH_2), 52.3 (NCH_2), 43.1 (NCH_3), 42.7 (NCH_3), 26.4 ($OCH_2\mathbf{C}H_2$), 25.4 (CH_2); ν_{max}/cm^{-1} (thin film) 2949, 2788, 1743, 1462, 1399, 1355, 1255, 1082, 922, 794; HRMS (ESI); calcd. for $C_{16}H_{24}N_3O_3^+$, 316.2595. Found: $[MH]^+$, 316.2599 (–1.4 ppm error).

2-Methoxycarbonylbenzyltriphenylphosphonium bromide (2.186)



To a solution of methyl 2-(bromomethyl)benzoate (2.29 g, 10.0 mmol) in DMF (20 mL) was added triphenylphosphine (2.89 g, 11.0 mmol) and the resulting solution was stirred at 60 °C for 18 h. The product was precipitated with ethyl acetate (40 mL), filtered and washed with ethyl acetate to yield the title compound (4.15 g, 85%) as a white solid. δ_H (400 MHz, $CDCl_3$) 7.87–7.74 (5H, m, ArH), 7.68–7.58 (12H, m, ArH), 7.50–7.45 (1H, m, ArH), 7.39–7.34 (1H, m, ArH), 5.98 (2H, d, $^2J_{H\text{-}P}$ = 15.0 Hz, CH_2), 3.48 (3H, s, CH_3). Characterisation data matched those reported in the literature.[122]

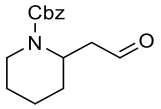
Benzyl 2-(2-hydroxyethyl)piperidine-1-carboxylate (2.188)



2-Piperidineethanol (1.29 g, 10.0 mmol) was dissolved in ethanol (13 mL) and to this was added potassium carbonate (2.76 g, 20.0 mmol) dissolved in water (13 mL). The solution was cooled to 0 °C before adding benzyl chloroformate (1.05 mL, 2.05 g, 12.0 mmol). The reaction was stirred for 15 mins at 0 °C then warmed to RT and stirred for a further 3 h. The product was extracted with DCM (3 x 50 mL) and combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 3:2 hexane:ethyl acetate) to yield the title compound (2.51 g, 95%) as a colourless oil. R_f 0.24 (3:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.38–7.28 (5H, m, ArH), 5.19–5.07 (2H, m, $PhCH_2$), 4.53–4.44 (1H, m, NCH), 4.10–3.98 (1H, m, NC**H**H'),

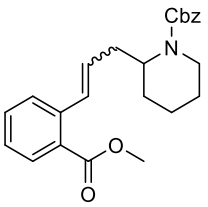
3.63–3.29 (3H, m, C**H**$_2$O**H**), 2.74 (1H, t, *J* = 13.0 Hz, NCH**H'**), 1.95 (1H, t, *J* = 13.0 Hz, C**H**H'), 1.79–1.35 (7H, m, CHH'). Characterisation data matched those reported in the literature.[123]

Benzyl 2-(2-oxoethyl)piperidine-1-carboxylate (2.189)



A round-bottom flask was charged with oxalyl chloride (0.870 mL, 1.26 g, 9.94 mmol) and DCM (4.7 mL) before being cooled to −78 °C. A solution of DMSO (1.80 mL, 1.94 g, 24.8 mmol) in DCM (5.6 mL) was then added dropwise and the resulting mixture was stirred for 5 minutes at −78 °C. A solution of benzyl 2-(2-hydroxyethyl)piperidine-1-carboxylate **2.188** (2.18 g, 8.28 mmol) in DCM (2.9 mL) was then added dropwise and the resulting mixture was stirred for 15 minutes at −78 °C before adding triethylamine (5.80 mL, 4.19 g, 41.4 mmol) dropwise. This was stirred for 5 minutes at −78 °C and then warmed to room temperature and stirred for 18 h. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (100mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 6:4 hexane:ethyl acetate) to yield the title compound (2.09 g, 96%) as a yellow oil. R_f 0.48 (6:4 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 9.71 (1H, s, CHO), 7.40–7.29 (5H, m, ArH), 5.12 (2H, s, CH_2Ph), 4.97–4.89 (1H, m, NCH), 4.14–4.00 (1H, m, NC**H**H'), 2.86 (1H, t, *J* = 13.5 Hz, NCH**H'**), 2.75 (1H, ddd, *J* = 15.5, 8.0, 3.0 Hz, C**H**H'CHO), 2.61 (1H, ddd, *J* = 15.5, 7.0, 2.0 Hz, CH**H'**CHO), 1.79–1.36 (6H, m, CHH'). Characterisation data matched those reported in the literature.[123]

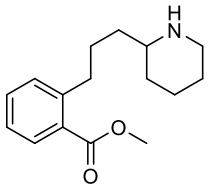
Benzyl 2-(3-(2-(methoxycarbonyl)phenyl)allyl)piperidine-1-carboxylate (2.190)



To a solution of sodium methoxide (297 mg, 5.50 mmol) in methanol (17 mL) was added 2-methoxycarbonylbenzyltriphenylphosphonium bromide **2.186** (2.46 g, 5.00 mmol) and the mixture was stirred at RT for 30 mins. The mixture was warmed to 50 °C before adding

benzyl 2-(2-oxoethyl)piperidine-1-carboxylate **2.189** (1.37 g, 5.25 mmol) and then the mixture was heated to reflux for 6 h. The mixture was concentrated *in vacuo* and then water (50 mL) was added, and the product was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 4:1 hexane:ethyl acetate) to yield the title compound (797 mg, 41%) as a 5:4 mixture of *Z*:*E* isomers and as a yellow oil. R_f 0.36 (4:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.94 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.86 (1H, d, *J* = 7.5 Hz, ArH), 7.49–7.24 (16H, m, ArH), 7.21 (1H, d, *J* = 16.0 Hz, ArCH=C**H** *E*-isomer), 6.93 (1H, d, *J* = 11.5 Hz, ArCH=C**H** *Z*-isomer), 6.12–5.98 (1H, m, ArC**H**=CH), 5.72–5.61 (1H, m, ArC**H**=CH), 5.14 (2H, s, $PhCH_2$), 5.10 (2H, s, $PhCH_2$), 4.56–4.35 (2H, m, NCH both isomers), 4.14–3.92 (2H, m, CHH'), 3.87 (3H, s, CH_3), 3.84 (3H, s, CH_3), 2.99–2.89 (1H, m, C**H**H'), 2.73–2.29 (5H, m, CHH'), 1.73–1.14 (12H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 167.9 (CO_2Me), 167.6 (CO_2Me), 155.7 (CO_2Bn), 155.5 (CO_2Bn), 139.4 (ArC), 138.8 (ArC), 137.2 (ArC), 137.1 (ArC), 132.2 (ArC), 131.7 (ArC), 131.2 (ArCH=**C**H), 130.8 (ArCH=**C**H), 130.5 (ArC), 130.4 (ArC), 130.0 (Ar**C**H=CH), 129.5 (ArC), 128.5 (ArC), 128.5 (ArC), 128.1 (ArC), 128.0 (ArC), 127.9 (Ar**C**H=CH, 2 x ArC), 127.8 (ArC), 127.6 (ArC), 127.0 (ArC), 126.8 (ArC), 67.0 (2 x $PhCH_2$), 52.1 (CH_3), 52.0 (CH_3), 51.0 (2 x NCH), 39.4 (CH_2), 39.3 (CH_2), 34.0 (CH_2), 28.6 (CH_2), 28.1 (CH_2), 27.7 (CH_2), 25.6 (CH_2), 25.4 (CH_2), 18.9 (CH_2), 18.8 (CH_2); ν_{max}/cm^{-1} (thin film) 2940, 1720, 1691, 1421, 1340, 1293, 1256, 1167, 1132, 1077, 966, 747, 698; HRMS (ESI); calcd. for $C_{24}H_{28}NO_4^+$, 394.2013. Found $[MH]^+$, 394.2021 (–2.0 ppm error).

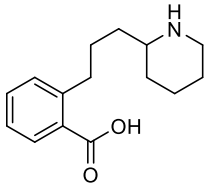
Methyl 2-(3-(piperidin-2-yl)propyl)benzoate (2.191)



To a solution of benzyl 2-(3-(2-(methoxycarbonyl)phenyl)allyl)piperidine-1-carboxylate **2.190** (163 mg, 0.414 mmol) in ethanol (2.8 mL) was added 10% palladium on carbon (16 mg). The reaction mixture was stirred under a hydrogen atmosphere at RT for 6 h. The suspension was filtered through Celite and the filtrate concentrated *in vacuo* to yield the title compound as a colourless oil (107 mg, 99%). δ_H (400 MHz, $CDCl_3$) 7.80 (1H, d, *J* = 7.5 Hz, ArH), 7.34 (1H, t, *J* = 7.5 Hz, ArH), 7.20–7.14 (2H, m, ArH), 3.82 (3H, s, CH_3), 3.05–2.76

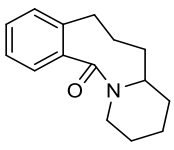
(4H, m, CHH' and NH), 2.57 (1H, td, *J* = 11.5, 3.0 Hz, CHH'), 2.49–2.40 (1H, m, NCH), 1.75–1.49 (5H, m, CHH'), 1.44–1.19 (4H, m, CHH'), 1.11–0.98 (1H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 168.1 (**C**O_2CH_3), 144.4 (ArC), 131.9 (ArC), 131.0 (ArC), 130.7 (ArC), 129.4 (ArC), 125.8 (ArC), 56.6 (NCH), 51.9 (CH_3), 47.0 (CH_2), 37.1 (CH_2), 34.5 (CH_2), 32.6 (CH_2), 28.1 (CH_2), 26.3 (CH_2), 24.8 (CH_2); ν_{max}/cm^{-1} (thin film) 2928, 2853, 1720, 1601, 1434, 1255, 1098, 1082, 751, 710; HRMS (ESI); calcd. for $C_{16}H_{24}NO_2^+$, 262.1802. Found: $[MH]^+$, 262.1804 (–1.1 ppm error).

2-(3-(Piperidin-2-yl)propyl)benzoic acid (2.184)



To a solution of methyl 2-(3-(piperidin-2-yl)propyl)benzoate **2.191** (530 mg, 2.03 mmol) in THF (4.1 mL) was added aq. LiOH (4.50 mL, 0.5 M, 2.23 mmol) and the mixture was refluxed for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (10:9:1 methanol:ethyl acetate:triethylamine) to yield the title compound (467 mg, 93%) as a white solid. R_f 0.33 (10:9:1 methanol:ethyl acetate:triethylamine); m.p. 210–213 °C; δ_H (400 MHz, $CDCl_3$) 7.83–7.77 (1H, m, ArH), 7.24–7.03 (3H, m, ArH), 3.80–3.69 (1H, m, CHH'), 3.39 (1H, br s, NH), 3.07–2.93 (1H, m, NCH), 2.79 (1H, t, *J* = 6.0 Hz, CHH'), 2.48–2.34 (1H, m, CHH'), 1.96–1.35 (11H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 176.2 (CO_2H), 140.8 (ArC), 137.8 (ArC), 130.3 (ArC), 130.0 (ArC), 129.1 (ArC), 126.0 (ArC), 54.7 (NCH), 44.1 (CH_2), 33.6 (CH_2), 32.8 (CH_2), 29.7 (CH_2), 27.0 (CH_2), 22.9 (CH_2), 22.6 (CH_2); ν_{max}/cm^{-1} (thin film) 3398, 2942, 2863, 2733, 2524, 1603, 1579, 1550, 1446, 1372, 909, 752, 727, 661; HRMS (ESI); calcd. for $C_{15}H_{22}NO_2^+$, 248.1645. Found: $[MH]^+$, 248.1651 (–2.3 ppm error).

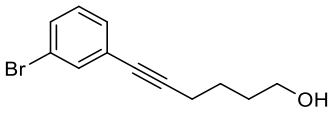
5,6,7,7*a*,8,9,10,11-Octahydro-13*H*-benzo[*f*]pyrido[1,2-*a*]azocin-13-one (2.185)



2-(3-(Piperidin-2-yl)propyl)benzoic acid **2.184** (256 mg, 1.04 mmol) was dissolved in DMF (10.4 mL) and to this was added DIPEA (0.910 mL, 672 mg, 5.20 mmol), EDC·HCl (318 mg, 1.66 mmol) and HOBt (224 mg, 1.66 mmol). The resulting mixture was stirred at RT for 24

h. The reaction mixture was diluted with ethyl acetate (50 mL) and then washed with brine (3 x 50 mL). The combined aqueous layers were then extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1:1 hexane:ethyl acetate) to yield the title compound (214 mg, 90%) as a yellow oil. R_f 0.46 (1:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.39 (1H, dd, *J* = 7.5, 1.5 Hz, ArH), 7.32 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 7.25 (1H, t, *J* = 7.5 Hz, ArH), 7.14 (1H, d, *J* = 7.5 Hz, ArH), 4.77 (1H, d, *J* = 13.5 Hz, NC**H**H'), 3.75 (1H, d, *J* = 10.0 Hz, NCH), 2.91 (1H, td, *J* = 13.0, 3.5 Hz, NCH**H'**), 2.82–2.75 (1H, m, CHH'), 2.68–2.59 (1H, m, CHH'), 2.16–2.00 (2H, m, CHH'), 1.81–1.74 (1H, m, CHH'), 1.62–1.40 (7H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 170.2 (CO) 139.7 (ArC), 135.8 (ArC), 129.6 (ArC), 129.0 (ArC), 127.0 (ArC), 126.3 (ArC), 52.7 (NCH), 36.5 (NCH_2), 32.5 (2 x CH_2), 29.6 (CH_2), 27.2 (CH_2), 25.1 (CH_2), 18.9 (CH_2); ν_{max}/cm^{-1} (thin film) 2932, 2858, 1628, 1453, 1421, 1282, 1136, 1020, 784, 754, 650; HRMS (ESI); calcd. for $C_{15}H_{20}NO^+$, 230.1539. Found: $[MH]^+$, 230.1541 (–0.6 ppm error).

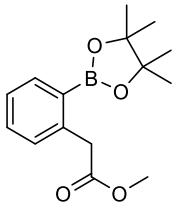
6-(3-Bromophenyl)hex-5-yn-1-ol (2.199)



To a suspension of bis(triphenylphosphine)palladium(II) dichloride (7 mg, 0.010 mmol) and copper(I) iodide (6 mg, 0.030 mmol) in degassed triethylamine (1.0 mL) was added 3-bromoiodobenzene (0.130 mL, 283 mg, 1.00 mmol) followed by 5-hexyn-1-ol (0.130 mL, 118 mg, 1.20 mmol). The reaction mixture was stirred at 60 °C for 2h. Diethyl ether (10 mL) was added and the resulting suspension was filtered through Celite. The filtrate was concentrated *in vacuo* and then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (251 mg, 99%) as a colourless oil. R_f 0.17 (8:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.52 (1H, t, *J* = 2.0 Hz, ArH), 7.39–7.35 (1H, d, *J* = 8.0 Hz, ArH), 7.31–7.27 (1H, d, *J* = 8.0 Hz, ArH), 7.11 (1H, t, *J* = 8.0 Hz, ArH), 3.66 (2H, t, *J* = 6.0 Hz, C**H**$_2$OH), 2.57 (1H, s, OH), 2.42 (2H, t, *J* = 6.5 Hz, C≡CCH_2), 1.75–1.60 (4H, m, CH_2C**H**$_2$C**H**$_2$$CH_2$); δ_C (101 MHz, $CDCl_3$) 134.3 (ArC), 130.7 (ArC), 130.1 (ArC), 129.7 (ArC), 125.9 (ArC), 122.0 (ArC), 91.6 (ArC≡**C**), 79.6 (Ar**C**≡C), 62.2 (CH_2OH), 31.8 (CH_2), 24.9 (CH_2), 19.2 (C≡C**C**H_2); ν_{max}/cm^{-1} (thin film) 3326, 2939, 2865, 2230, 1590, 1555, 1473, 1404, 1065,

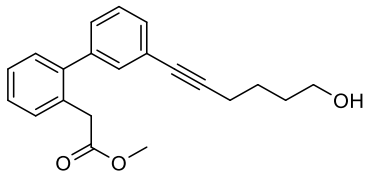
995, 879, 780, 729, 681; HRMS (ESI); calcd. for $C_{12}H_{13}{}^{79}BrONa^{+}$, 275.0042. Found: $[MNa]^{+}$, 275.0029 (4.8 ppm error).

Methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (2.200)



To a solution of methyl 2-(2-bromophenyl)acetate (0.790 mL, 1.15 g, 5.00 mmol) in 1,4-dioxane (18 mL) was added bis(pinacolato)diboron (1.40 g, 5.50 mmol), potassium acetate (1.82 g, 18.5 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (220 mg, 0.300 mmol). The resulting mixture was heated to reflux for 4 h. The reaction mixture was diluted with ethyl acetate, filtered through Celite (ethyl acetate) and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 8:2 DCM:hexane) to yield the title compound (718 mg, 52%) as an off-white solid. δ_H (400 MHz, $CDCl_3$) 7.84 (1H, d, *J* = 7.5 Hz, ArH), 7.40 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 7.30–7.26 (1H, m, ArH), 7.20 (1H, d, *J* = 7.5 Hz, ArH), 3.99 (2H, s, CH_2), 3.67 (3H, s, OCH_3), 1.33 (12H, s, $C(CH_3)_2$). Characterisation data matched those reported in the literature.[124]

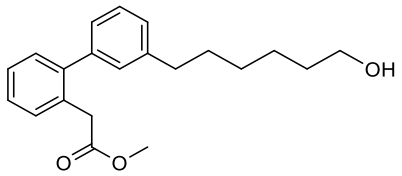
Methyl 2-(3'-(6-hydroxyhex-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)acetate (2.201)



A dry round bottom flask was charged with 6-(3-bromophenyl)hex-5-yn-1-ol **2.199** (100 mg, 0.395 mmol), methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate **2.200** (173 mg, 0.593 mmol) and tetrakis(triphenylphosphine)palladium (23 mg, 0.0198 mmol). To this was added caesium carbonate (0.660 mL, 2.1 M in water, 1.38 mmol) and 1,2-dimethoxyethane (3.3 mL) and the reaction mixture was heated to 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* and redissolved in ethyl acetate (20 mL). The organic layer was washed with water (20 mL) and brine (20 mL) and the combined aqueous layers were extracted with ethyl acetate (2 x 20 mL). The combined organic layers were

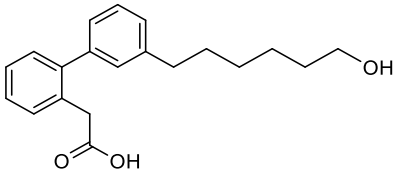
dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 7:3 hexane:ethyl acetate) to yield the title compound (97 mg, 76%) as a colourless oil. R_f 0.27 (7:3 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.41–7.30 (6H, m, ArH), 7.27–7.20 (2H, m, ArH), 3.71 (2H, t, *J* = 6.0 Hz, OCH_2), 3.64 (3H, s, CH_3), 3.59 (2H, s, C**H**$_2$CO$_2$Me), 2.47 (2H, t, *J* = 6.5 Hz, C≡CCH_2), 1.81–1.65 (4H, m, 2 x CH_2); δ_C (101 MHz, $CDCl_3$) 172.4 (CO), 141.7 (ArC), 141.1 (ArC), 132.4 (ArC), 131.7 (ArC), 130.4 (ArC), 130.3 (ArC), 130.1 (ArC), 128.5 (ArC), 128.2 (ArC), 127.8 (ArC), 127.3 (ArC), 123.9 (ArC), 90.3 (ArC≡**C**), 80.8 (Ar**C**≡C), 62.3 (OCH_2), 52.0 (CH_3), 38.7 (**C**H_2CO_2Me), 31.9 (CH_2), 25.0 (CH_2), 19.2 (C≡C**C**H_2); ν_{max}/cm^{-1} (thin film) 3393, 2945, 1736, 1596, 1474, 1434, 1338, 1252, 1209, 1159, 1062, 1003, 900, 800, 760, 703; HRMS (ESI); calcd. for $C_{21}H_{23}O_3^+$, 323.1642. Found $[MH]^+$, 323.1644 (–0.7 ppm error).

Methyl 2-(3'-(6-hydroxyhexyl)-[1,1'-biphenyl]-2-yl)acetate (2.202)



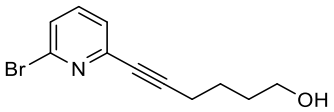
To a solution of methyl 2-(3'-(6-hydroxyhex-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)acetate **2.201** (94 mg, 0.292 mmol) in ethanol (1.9 mL) was added 10% palladium on carbon (9 mg). The reaction mixture was stirred under a hydrogen atmosphere at RT for 16 h. The suspension was filtered through Celite and the filtrate concentrated *in vacuo* to yield the title compound (92 mg, 97%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.39–7.28 (5H, m, ArH), 7.20–7.12 (3H, m, ArH), 3.66–3.60 (7H, m, OCH_2, C**H**$_2$CO$_2$C**H**$_3$), 2.67 (2H, t, *J* = 8.0 Hz, ArCH_2), 1.72–1.54 (4H, m, 2 x CH_2), 1.44–1.36 (4H, m, 2 x CH_2); δ_C (101 MHz, $CDCl_3$) 172.6 (CO), 142.7 (2 x ArC), 141.0 (ArC), 131.8 (ArC), 130.4 (ArC), 130.2 (ArC), 129.4 (ArC), 128.2 (ArC), 127.5 (ArC), 127.3 (ArC), 127.2 (ArC), 126.6 (ArC), 62.9 (OCH_2), 52.0 (CH_3), 38.9 (**C**H_2CO_2), 35.9 (ArCH_2), 32.7 (CH_2), 31.4 (CH_2), 29.1 (CH_2), 25.7 (CH_2); ν_{max}/cm^{-1} (thin film) 3369, 2929, 2856, 1736, 1600, 1476, 1434, 1338, 1249, 1211, 1157, 1053, 1005, 906, 796, 756, 709; HRMS (ESI); calcd. for $C_{21}H_{27}O_3^+$, 327.1955. Found $[MH]^+$, 327.1961 (–1.8 ppm error).

2-(3'-(6-Hydroxyhexyl)-[1,1'-biphenyl]-2-yl)acetic acid (2.194)



To a solution of methyl 2-(3'-(6-hydroxyhexyl)-[1,1'-biphenyl]-2-yl)acetate **2.202** (216 mg, 0.662 mmol) in THF (1.3 mL) was added lithium hydroxide (1.50 mL, 0.5 M in water, 0.728 mmol) and the reaction mixture was heated to reflux for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 10:9:1 ethyl acetate:hexane:acetic acid) to yield the title compound (182 mg, 88%) as a yellow oil. R_f 0.58 (10:9:1 ethyl acetate:hexane:acetic acid); δ_H (400 MHz, $CDCl_3$) 7.37–7.27 (5H, m, ArH), 7.19–7.10 (3H, m, ArH), 3.66–3.59 (4H, m, OCH_2, C**H**$_2CO_2H$), 2.64 (2H, t, *J* = 7.5 Hz, $ArCH_2$), 1.67 (2H, p, *J* = 7.5 Hz, CH_2), 1.55 (2H, p, *J* = 6.5 Hz, CH_2), 1.43–1.30 (4H, m, 2 x CH_2); δ_C (101 MHz, $CDCl_3$) 176.4 (CO_2H), 142.9 (ArC), 142.7 (ArC), 141.1 (ArC), 131.6 (ArC), 130.7 (ArC), 130.3 (ArC), 129.6 (ArC), 128.3 (ArC), 127.6 (ArC), 127.5 (ArC), 127.4 (ArC), 126.5 (ArC), 62.9 (OCH_2), 38.8 (**C**H_2CO_2H), 35.5 ($ArCH_2$), 32.1 (CH_2), 31.0 (CH_2), 28.5 (CH_2), 25.4 (CH_2); ν_{max}/cm^{-1} (thin film) 3420, 2931, 2856, 1709, 1477, 1413, 1228, 1053, 797, 759, 709; HRMS (ESI); calcd. for $C_{20}H_{24}O_3Na^+$, 335.1618. Found: $[MNa]^+$, 335.1623 (–1.6 ppm error).

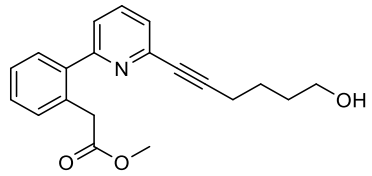
6-(6-Bromopyridin-2-yl)hex-5-yn-1-ol (2.204)



To a solution of 2,6-dibromopyridine (1.18 g, 5.00 mmol) in THF (20 mL) was added 5-hexyne-1-ol (0.550 mL, 491 mg, 5.00 mmol), triethylamine (4.90 mL, 3.54 g, 35.0 mmol), copper(I) iodide (95 mg, 0.500 mmol) and tetrakis(triphenylphosphine)palladium (289 mg, 0.250 mmol) and the reaction mixture was stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo*, redissolved in DCM (50 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 7:3 hexane:ethyl acetate) to yield the title compound (684 mg, 54%) as a yellow oil. R_f 0.21 (7:3 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.45 (1H, t, *J* = 7.5 Hz, ArH), 7.36 (1H, d, *J* = 7.5 Hz, ArH), 7.29 (1H, d, *J*

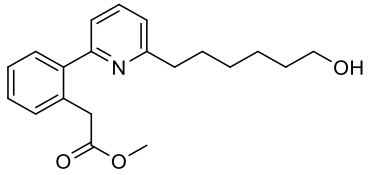
= 7.5 Hz, ArH), 3.70–3.64 (2H, m, OCH_2), 2.49–2.43 (2H, m, $ArCH_2$), 1.76–1.65 (4H, m, 2 x CH_2); δ_C (101 MHz, $CDCl_3$) 144.3 (ArC), 141.5 (ArC), 138.4 (ArC), 127.1 (ArC), 125.8 (ArC), 92.8 (ArC≡**C**), 79.6 (Ar**C**≡C), 62.2 (OCH_2), 31.9 (CH_2), 24.6 (CH_2), 19.2 (C≡C**C**H_2); ν_{max}/cm^{-1} (thin film) 3352, 2937, 2865, 2229, 1571, 1543, 1428, 1288, 1157, 1122, 1062, 980, 791, 728, 658; HRMS (ESI); calcd. for $C_{11}H_{13}{}^{79}BrNO^+$, 254.0175. Found: $[MH]^+$, 254.0173 (0.6 ppm error).

Methyl 2-(2-(6-(6-hydroxyhex-1-yn-1-yl)pyridin-2-yl)phenyl)acetate (2.205)



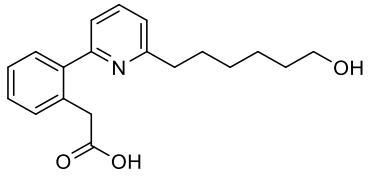
A dry round bottom flask was charged with 6-(6-bromopyridin-2-yl)hex-5-yn-1-ol **2.204** (684 mg, 2.69 mmol), methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate **2.200** (1.18 g, 4.04 mmol) and tetrakis(triphenylphosphine)palladium (156 mg, 0.135 mmol). To this was added caesium carbonate (4.50 mL, 2.1 M in water, 9.42 mmol) and 1,2-dimethoxyethane (22 mL) and the reaction mixture was heated to 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* and redissolved in ethyl acetate (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL) and the combined aqueous layers were extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 1:1 hexane:ethyl acetate) to yield the title compound (573 mg, 66%) as a colourless oil. R_f 0.28 (1:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.68 (1H, t, *J* = 8.0 Hz, ArH), 7.43–7.31 (6H, m, ArH), 3.79 (2H, s, CH_2CO_2), 3.65 (2H, t, *J* = 6.0 Hz, OCH_2), 3.60 (3H, s, CH_3), 2.47 (2H, t, *J* = 6.5 Hz, C≡CCH_2), 1.77–1.64 (4H, m, 2 x CH_2); δ_C (101 MHz, $CDCl_3$) 172.4 (**C**O_2Me), 159.6 (ArC), 143.11 (ArC), 140.2 (ArC), 136.7 (ArC), 132.5 (ArC), 131.3 (ArC), 129.9 (ArC), 128.7 (ArC), 127.5 (ArC), 125.1 (ArC), 122.8 (ArC), 90.6 (ArC≡**C**), 81.0 (Ar**C**≡C), 62.3 (OCH_2), 52.0 (CH_3), 39.2 (**C**H_2CO_2Me), 31.9 (CH_2), 24.7 (CH_2), 19.2 (C≡C**C**H_2); ν_{max}/cm^{-1} (thin film) 3380, 2946, 2229, 1733, 1562, 1441, 1338, 1251, 1212, 1159, 1062, 1007, 816, 763; HRMS (ESI); calcd. for $C_{20}H_{22}NO_3^+$, 324.1594. Found: $[MH]^+$, 324.1599 (–1.6 ppm error).

Methyl 2-(2-(6-(6-hydroxyhexyl)pyridin-2-yl)phenyl)acetate (2.206)



To a solution of methyl 2-(2-(6-(6-hydroxyhex-1-yn-1-yl)pyridin-2-yl)phenyl)acetate **2.205** (537 mg, 1.66 mmol) in ethanol (11 mL) was added 10% palladium on carbon (54 mg). The reaction mixture was stirred under a hydrogen atmosphere at RT for 18 h. The reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to yield the title compound (506 mg, 93%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 7.67 (1H, t, *J* = 7.5 Hz, ArH), 7.46–7.42 (1H, m, ArH), 7.39–7.33 (3H, m, ArH), 7.29–7.26 (1H, m, ArH), 7.10 (1H, d, *J* = 7.5 Hz, ArH), 3.86 (2H, s, CH_2CO_2), 3.63–3.56 (5H, m, OCH_2, CH_3), 2.83 (2H, t, *J* = 8.0 Hz, $ArCH_2$), 1.81–1.72 (2H, m, CH_2), 1.60–1.52 (2H, m, CH_2), 1.45–1.37 (4H, m, 2 x CH_2); δ_C (101 MHz, $CDCl_3$) 172.5 (**C**O_2Me), 161.7 (ArC), 158.9 (ArC), 140.6 (ArC), 137.0 (ArC), 132.6 (ArC), 131.5 (ArC), 130.0 (ArC), 128.6 (ArC), 127.5 (ArC), 121.3 (ArC), 120.9 (ArC), 62.9 (OCH_2), 51.9 (CH_3), 39.4 (**C**H_2CO_2Me), 38.3 ($ArCH_2$), 32.7 (CH_2), 29.9 (CH_2), 29.2 (CH_2), 25.7 (CH_2); ν_{max}/cm^{-1} (thin film) 3370, 2929, 2857, 1734, 1589, 1570, 1446, 1339, 1249, 1212, 1159, 1055, 1004, 813, 760; HRMS (ESI); calcd. for $C_{20}H_{26}NO_3^+$, 328.1907. Found: $[MH]^+$, 328.1907 (–0.1 ppm error).

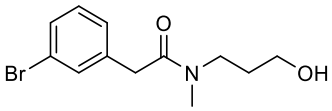
2-(2-(6-(6-Hydroxyhexyl)pyridin-2-yl)phenyl)acetic acid (2.195)



To a solution of methyl 2-(2-(6-(6-hydroxyhexyl)pyridin-2-yl)phenyl)acetate **2.206** (493 mg, 1.50 mmol) in THF (3.0 mL) was added lithium hydroxide (3.30 mL, 0.5 M in water, 1.65 mmol) and the mixture was heated to reflux for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 99:1 ethyl acetate:acetic acid) to yield the title compound (391 mg, 83%) as a colourless oil. R_f 0.42 (99:1 ethyl acetate:acetic acid); δ_H (400 MHz, $CDCl_3$) 7.90 (1H, t, *J* = 8.0 Hz, ArH), 7.56–7.48 (3H, m, ArH), 7.46–7.37 (2H ,m, ArH), 7.31 (1H, d, *J* = 7.5 Hz, ArH), 3.67 (2H, s, C**H**$_2CO_2H$), 3.62 (2H, t, *J* = 6.5 Hz, OCH_2), 2.91 (2H, t, *J* = 8.0 Hz, $ArCH_2$), 1.78–1.69 (2H, m, CH_2), 1.60–

1.51 (2H, m, CH_2), 1.44–1.37 (4H, m, 2 x CH_2); δ_C (101 MHz, $CDCl_3$) 173.0 (CO_2H), 161.0 (ArC), 157.1 (ArC), 139.7 (ArC), 137.6 (ArC), 133.1 (ArC), 131.7 (ArC), 130.7 (ArC), 130.0 (ArC), 127.9 (ArC), 122.6 (ArC), 122.5 (ArC), 62.8 (OCH_2), 42.2 (**C**H_2CO_2H), 36.5 ($ArCH_2$), 32.5 (CH_2), 30.3 (CH_2), 29.0 (CH_2), 25.4 (CH_2); ν_{max}/cm^{-1} (thin film) 3416, 2930, 2857, 1720, 1598, 1578, 1500, 1449, 1256, 1145, 1053, 1014, 816, 764, 726, 697; HRMS (ESI); calcd. for $C_{19}H_{24}NO_3^+$, 314.1751. Found: $[MH]^+$, 314.1750 (0.2 ppm error).

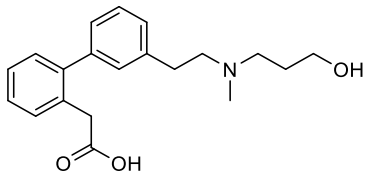
2-(3-Bromophenyl)-*N*-(3-hydroxypropyl)-*N*-methylacetamide (2.208)



A solution of 3-bromophenylacetic acid (1.08 g, 5.00 mmol) in DCM (6.7 mL) was cooled to 0 °C before dropwise addition of thionyl chloride (0.550 mL, 892 mg, 7.50 mmol) and *N*,*N*-dimethylformamide (1 drop) and the reaction mixture was warmed to RT and stirred for 3 h. The reaction mixture was concentrated *in vacuo* and then redissolved in DCM (6.7 mL) before cooling to 0 °C and adding 3-methylamino-1-propanol (1.10 mL, 1.07 g, 12.0 mmol). The reaction mixture was warmed to RT and stirred for 2h. The reaction was quenched with water (40 mL) and extracted with DCM (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, ethyl acetate) to yield the title compound (1.27 g, 89%) as a 4:1 (A:B) mixture of rotamers and as a colourless oil. R_f 0.29 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.42–7.32 (4H, m, 2 x ArH rotamer A, 2 x ArH rotamer B), 7.20–7.13 (4H, m, 2 x ArH rotamer A, 2 x ArH rotamer B), 3.72 (2H, s, $ArCH_2$ rotamer B), 3.68 (2H, s, $ArCH_2$ rotamer A), 3.59 (2H, t, *J* = 5.5 Hz, OCH_2 rotamer B), 3.52 (2H, t, *J* = 6.0 Hz, NCH_2 rotamer A), 3.45 (2H, t, *J* = 5.5 Hz, OCH_2 rotamer A), 3.41 (2H, t, *J* = 6.5 Hz, NCH_2 rotamer B), 2.98 (3H, s, NCH_3 rotamer A), 2.91 (3H, s, NCH_3 rotamer B), 1.75–1.65 (4H, m, $OCH_2C\mathbf{H}_2$ both rotamers); δ_C (101 MHz, $CDCl_3$) 171.8 (NCO rotamer A), 170.6 (NCO rotamer B), 137.9 (ArC rotamer B), 136.9 (ArC rotamer A), 132.0 (ArC rotamer B), 131.9 (ArC rotamer A), 130.3 (ArC rotamer A), 130.2 (ArC rotamer A), 130.1 (ArC rotamer B), 129.9 (ArC rotamer B), 127.8 (ArC rotamer B), 127.6 (ArC rotamer A), 122.7 (ArC rotamer A), 122.5 (ArC rotamer B), 58.5 (OCH_2 rotamer B), 58.1 (OCH_2 rotamer A), 46.9 (NCH_2 rotamer B), 44.4 (NCH_2 rotamer A), 40.4 ($ArCH_2$ rotamer A), 39.8 ($ArCH_2$ rotamer B), 35.9 (NCH_3 rotamer A), 33.5 (NCH_3 rotamer B), 30.9 ($OCH_2\mathbf{C}H_2$

rotamer B), 29.5 (OCH_2**C**H_2 rotamer A); v_{max}/cm^{-1} (thin film) 3393, 2938, 2869, 1619, 1567, 1473, 1428, 1403, 1261, 1166, 1071, 943, 857, 7634, 683, 602; HRMS (ESI); calcd. for $C_{12}H_{17}{}^{79}BrNO_2{}^+$, 286.0437. Found: $[MH]^+$, 286.0438 (–0.3 ppm error).

2-(3'-(2-((3-Hydroxypropyl)(methyl)amino)ethyl)-[1,1'-biphenyl]-2-yl)acetic acid (2.196)



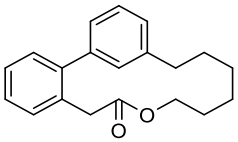
Lithium aluminium hydride (5.00 mL, 2.4 M in THF, 11.9 mmol) was diluted with THF (50 mL) and cooled to 0 °C. To this was added a solution of 2-(3-bromophenyl)-*N*-(3-hydroxypropyl)-*N*-methylacetamide **2.208** (1.13 g, 3.95 mmol) in THF (20 mL) dropwise and the reaction mixture was heated to reflux for 2 h. The reaction was quenched with ethyl acetate followed by 4 M aq. NaOH (50 mL) and sat. aq. Rochelle salt (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 19:1 ethyl acetate:triethylamine) to yield mixture of 3-((3-bromophenethyl)(methyl)amino)propan-1-ol **2.209a** and 3-(methyl(phenethyl)amino)propan-1-ol **2.209b** (606 mg) which was used in the next step without further purification.

A dry round bottom flask was charged with the impure 3-((3-bromophenethyl)(methyl)amino)propan-1-ol **2.209a** (606 mg), methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate **2.200** (824 mg, 2.82 mmol) and tetrakis(triphenylphosphine)palladium (108 mg, 0.094 mmol). To this was added caesium carbonate (3.10 mL, 2.1 M in water, 6.59 mmol) and 1,2-dimethoxyethane (16 mL) and the reaction mixture was heated to 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* and redissolved in ethyl acetate (30 mL). The organic layer was washed with water (30 mL) and brine (30 mL) and the combined aqueous layers were extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 19:1 ethyl acetate:triethylamine) to yield a mixture of methyl 2-(3'-(2-((3-hydroxypropyl)(methyl)amino)ethyl)-[1,1'-biphenyl]-2-yl)acetate **2.210** and 3-

(methyl(phenethyl)amino)propan-1-ol **2.209b** (396 mg) which was used in the next step without further purification.

To a solution of the impure methyl 2-(3'-(2-((3-hydroxypropyl)(methyl)amino)ethyl)-[1,1'-biphenyl]-2-yl)acetate **2.210** (396 mg) in THF (1.9 mL) was added lithium hydroxide (3.30 mL, 0.5 M in water, 1.66 mmol) and the reaction mixture was heated to reflux for 18 h. The reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 10:9:1 methanol:ethyl acetate:triethylamine) to yield the title compound (167 mg, 13% over 3-steps) as a colourless oil. R_f 0.16 (10:9:1 methanol:ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.37–7.33 (1H, m, ArH), 7.29–7.17 (6H, m, ArH), 7.08–7.04 (1H, m, ArH), 3.59 (2H, t, *J* = 5.5 Hz, OCH_2), 3.46 (2H, s, C**H**$_2CO_2H$), 3.02–2.80 (6H, m, $ArCH_2$, 2 x NCH_2), 2.47 (3H, s, CH_3), 1.79–1.70 (2H, m, OCH_2C**H**$_2$); δ_C (101 MHz, $CDCl_3$) 177.5 (CO_2H), 142.1 (ArC), 141.9 (ArC), 137.4 (ArC), 134.8 (ArC), 131.1 (ArC), 130.0 (ArC), 129.8 (ArC), 128.6 (ArC), 127.7 (ArC), 127.5 (ArC), 127.3 (ArC), 126.5 (ArC), 60.3 (OCH_2), 57.6 (NCH_2), 54.6 (NCH_2), 41.8 (**C**H_2CO_2H), 40.3 (CH_3), 31.4 ($ArCH_2$), 27.3 (OCH_2**C**H_2); ν_{max}/cm^{-1} (thin film) 3312, 2923, 1579, 1475, 1423, 1366, 1260, 1062, 907, 800, 757, 726, 643; HRMS (ESI); calcd. for $C_{20}H_{26}NO_3^+$, 328.1907. Found: $[MH]^+$, 328.1906 (0.5 ppm error).

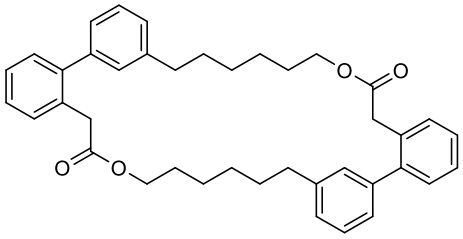
5-Oxa-1(1,3),2(1,2)-dibenzenacycloundecaphan-4-one (2.211)



A round-bottom flask was charged with 2-(3'-(6-hydroxyhexyl)-[1,1'-biphenyl]-2-yl)acetic acid **2.194** (96 mg, 0.307 mmol) and MeCN (3.1 mL). To this was added DIPEA (0.270 mL, 199 mg, 1.54 mmol), EDC·HCl (88 mg, 0.461 mmol) and HOBt (62 mg, 0.461 mmol) and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 9:1 hexane:ethyl acetate) to yield the title compound (19 mg, 21%) as a white solid. R_f 0.57 (9:1 hexane:ethyl acetate); m.p. 75–79 °C; δ_H (400 MHz, $CDCl_3$) 7.43–7.31 (4H, m, ArH), 7.30–7.26 (1H, m, ArH), 7.22–7.18 (1H, m, ArH), 7.14–7.08 (2H ,m, ArH), 4.16–4.12 (2H, m, OCH_2), 3.56 (2H, s, CH_2CO_2), 2.74–2.70 (2H, m, $ArCH_2$), 1.78–1.71 (2H, m, CH_2), 1.66–1.58 (2H, m, CH_2), 1.44–1.28 (4H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 172.3 (CO), 142.9 (ArC), 142.1 (ArC), 141.2 (ArC),

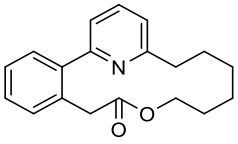
131.9 (ArC), 131.2 (ArC), 130.1 (ArC), 129.8 (ArC), 128.6 (ArC), 127.9 (ArC), 127.6 (ArC), 127.3 (ArC), 126.3 (ArC), 65.9 (OCH_2), 39.2 (**C**H_2CO_2), 34.5 ($ArCH_2$), 28.9 (CH_2), 27.4 (CH_2), 27.3 (CH_2), 26.6 (CH_2); ν_{max}/cm^{-1} (thin film) 3022, 2924, 2857, 1734, 1599, 1476, 1421, 1331, 1206, 1152, 1046, 977, 796, 755, 709; HRMS (ESI); calcd. for $C_{20}H_{23}O_2^+$, 295.1693. Found: $[MH]^+$, 295.1692 (0.0 ppm error).

5,16-Dioxa-1,12(1,3),2,13(1,2)-tetrabenzenacyclodocosaphane-4,15-dione (2.212)



Following the above procedure, the title compound (29 mg, 32%) was obtained as a white solid. R_f 0.33 (9:1 hexane:ethyl acetate); m.p. 130–134 °C; δ_H (400 MHz, $CDCl_3$) 7.28–7.26 (10H, m, ArH), 7.16–7.09 (6H, m, ArH), 3.99 (4H, t, *J* = 6.5 Hz, OCH_2), 3.60 (4H, s, CH_2CO_2), 2.61 (4H, t, *J* = 7.5 Hz, $ArCH_2$), 1.66–1.49 (8H, m, CH_2), 1.38–1.23 (8H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 172.2 (CO), 142.7 (ArC), 142.4 (ArC), 141.2 (ArC), 132.0 (ArC), 130.8 (ArC), 130.2 (ArC), 129.5 (ArC), 128.4 (ArC), 127.6 (ArC), 127.3 (2 x ArC), 126.7 (ArC), 65.0 (OCH_2), 39.2 (**C**H_2CO_2), 36.0 ($ArCH_2$), 31.5 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 26.0 (CH_2); ν_{max}/cm^{-1} (thin film) 3032, 2928, 2856, 1734, 1600, 1475, 1421, 1334, 1245, 1207, 1156, 984, 910, 796, 756, 709; HRMS (ESI); calcd. for $C_{40}H_{44}O_4Na^+$, 611.3132. Found $[MNa]^+$, 611.3130 (0.6 ppm error).

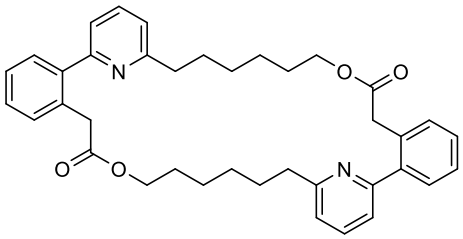
5-Oxa-1(2,6)-pyridina-2(1,2)-benzenacycloundecaphan-4-one (2.213)



A round-bottom flask was charged with 2-(2-(6-(6-hydroxyhexyl)pyridin-2-yl)phenyl)acetic acid **2.195** (391 mg, 1.25 mmol) and MeCN (12.5 mL). To this was added DIPEA (1.10 mL, 808 mg, 6.25 mmol), EDC·HCl (360 mg, 1.88 mmol) and HOBt (254 mg, 1.88 mmol) and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 4:1 hexane:ethyl acetate) to yield the title compound (97 mg, 26%) as a colourless oil. R_f 0.51 (4:1

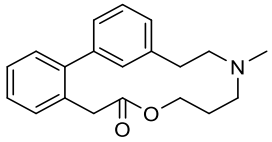
hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.68 (1H, t, *J* = 8.0 Hz, ArH), 7.50–7.46 (1H ,m, ArH), 7.41–7.30 (4H, m, ArH), 7.11 (1H, d, *J* = 8.0 Hz, ArH), 4.08–4.04 (2H, m, OCH_2), 4.02 (2H, s, CH_2CO_2), 2.94–2.88 (2H, m, $ArCH_2$), 1.92–1.84 (2H, m, CH_2), 1.70–1.64 (2H, m, CH_2), 1.52–1.43 (2H, m, CH_2), 1.35–1.26 (2H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 171.7 (CO), 161.3 (ArC), 159.4 (ArC), 140.4 (ArC), 136.9 (ArC), 132.4 (ArC), 132.3 (ArC), 130.1 (ArC), 128.3 (ArC), 127.5 (ArC), 121.0 (ArC), 120.8 (ArC), 63.9 (OCH_2), 39.6 (CH_2CO_2), 36.6 ($ArCH_2$), 27.7 (CH_2), 26.8 (CH_2), 25.7 (CH_2), 24.7 (CH_2); ν_{max}/cm^{-1} (thin film) 2926, 2857, 1737, 1588, 1570, 1445, 1344, 1208, 1152, 1039, 989, 909, 811, 757, 727, 699, 630; HRMS (ESI); calcd. for $C_{19}H_{22}NO_2^+$, 296.1645. Found: $[MH]^+$, 296.1644 (0.2 ppm error).

5,16-Dioxa-1,12(2,6)-dipyridina-2,13(1,2)-dibenzenacyclodocosaphane-4,15-dione (2.214)



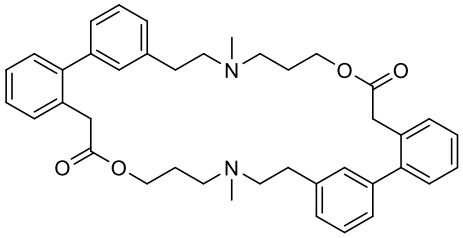
Following the above procedure, the title compound (35 mg, 9%) was obtained as a white solid. R_f 0.17 (4:1 hexane:ethyl acetate); m.p. 128–128 °C; δ_H (400 MHz, $CDCl_3$) 7.66 (2H, t, *J* = 8.0 Hz, ArH), 7.45–7.41 (1H, m, ArH), 7.39–7.34 (6H, m, ArH), 7.30–7.26 (2H, m, ArH), 7.06 (2H, d, *J* = 8.0 Hz, ArH), 3.96 (4H, t, *J* = 7.0 Hz, OCH_2), 3.93 (4H, s, CH_2CO_2), 2.82–2.76 (4H, m, $ArCH_2$), 1.79–1.70 (4H, m, CH_2), 1.58–1.49 (4H, m, CH_2), 1.40–1.28 (8H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 172.1 (CO), 161.3 (ArC), 159.3 (ArC), 140.6 (ArC), 137.0 (ArC), 132.9 (ArC), 132.0 (ArC), 129.9 (ArC), 128.5 (ArC), 127.5 (ArC), 121.2 (ArC), 120.7 (ArC), 64.7 (OCH_2), 39.4 (CH_2CO_2), 38.4 ($ArCH_2$), 29.8 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 26.0 (CH_2); ν_{max}/cm^{-1} (thin film) 2928, 2857, 1729, 1589, 1570, 1446, 1418, 1339, 1208, 1155, 1041, 990, 909, 812, 758, 728, 630; HRMS (ESI); calcd. for $C_{38}H_{43}N_2O_2^+$, 591.3217. Found: $[MH]^+$, 591.3221 (–0.6 ppm error).

5-Methyl-9-oxa-5-aza-1(1,2),2(1,3)-dibenzenacycloundecaphan-10-one (2.215)



A round-bottom flask was charged with 2-(3'-(2-((3-hydroxypropyl)(methyl)amino)ethyl)-[1,1'-biphenyl]-2-yl)acetic acid **2.196** (167 mg, 0.510 mmol) and MeCN (5.1 mL). To this was added DIPEA (0.440 mL, 330 mg, 2.55 mmol), EDC·HCl (147 mg, 0.765 mmol) and HOBt (103 mg, 0.765 mmol) and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 10:9:1 hexane:ethyl acetate:triethylamine) to yield the title compound (37 mg, 23%) as a colourless oil. R_f 0.60 (10:9:1 hexane:ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 7.39–7.29 (5H, m, ArH), 7.27–7.25 (1H, m, ArH), 7.21–7.18 (1H, m, ArH), 7.16–7.13 (1H, m, ArH), 3.96–3.92 (2H, m, OCH_2), 3.67 (2H, s, CH_2CO_2), 2.86–2.75 (4H, m, $ArCH_2$, NCH_2), 2.29 (2H, t, J = 6.5 Hz, NCH_2), 2.22 (3H, s, NCH_3), 1.69–1.61 (2H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 171.9 (CO), 142.6 (ArC), 141.4 (ArC), 141.3 (ArC), 132.2 (ArC), 131.3 (ArC), 130.3 (ArC), 129.7 (ArC), 128.4 (ArC), 127.5 (3 x ArC), 126.6 (ArC), 62.8 (OCH_2), 58.3 (NCH_2), 53.8 (NCH_2), 42.5 (NCH_3), 39.9 (**C**H_2CO_2), 35.0 ($ArCH_2$), 26.2 (CH_2); ν_{max}/cm^{-1} (thin film) 2923, 2847, 2788, 1732, 1600, 1475, 1421, 1355, 1332, 1209, 1158, 1039, 908, 792, 755, 708, 625; HRMS (ESI); calcd. for $C_{20}H_{24}NO_2^+$, 310.1802. Found: $[MH]^+$, 310.1809 (–2.3 ppm error).

9,20-Dimethyl-5,16-dioxa-9,20-diaza-1,12(1,2),2,13(1,3)-tetrabenzenacyclodocosaphane-4,15-dione (2.216)



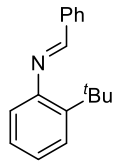
Following the above procedure, the title compound (32 mg, 20%) was obtained as a white solid. R_f 0.30 (10:9:1 hexane:ethyl acetate:triethylamine); m.p. 91–94 °C; δ_H (400 MHz, $CDCl_3$) 7.39–7.25 (10H, m, ArH), 7.17–7.10 (6H, m, ArH), 4.04 (4H, t, J = 6.5 Hz, OCH_2), 3.59 (4H, s, CH_2CO_2), 2.77–2.71 (4H, m, $ArCH_2$), 2.63–2.56 (4H, m, NCH_2), 2.39–2.33 (4H, m, NCH_2), 2.26 (6H, s, NCH_3), 1.72 (4H, p, J = 6.5 Hz, CH_2); δ_C (101 MHz, $CDCl_3$) 172.1 (CO), 142.6

(ArC), 141.3 (ArC), 140.4 (ArC), 132.0 (ArC), 130.7 (ArC), 130.2 (ArC), 129.7 (ArC), 128.4 (ArC), 127.7 (ArC), 127.6 (ArC), 127.3 (ArC), 126.9 (ArC), 63.2 (OCH_2), 59.5 (NCH_2), 53.9 (NCH_2), 42.2 (NCH_3), 39.2 (**C**H_2CO_2), 33.8 ($ArCH_2$), 26.6 (CH_2); v_{max}/cm^{-1} (thin film) 2950, 2847, 2792, 1731, 1600, 1475, 1380, 1335, 1245, 1207, 1155, 1038, 909, 798, 756, 729, 709, 645; HRMS (ESI); calcd. for $C_{40}H_{47}N_2O_4^+$, 619.3530. Found: $[MH]^+$, 619.3524 (1.1 ppm error).

General Procedure for the Preparation of Acyl Chlorides.

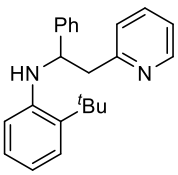
To a suspension of carboxylic acid (4.00 mmol) in DCM (20 mL) was added DMF (4 drops) followed by oxalyl chloride (12.0 mmol). The resulting solution was stirred at room temperature for 1–4 h. The reaction mixture was concentrated *in vacuo* and the products were used without further purification.

***N*-(2-(*tert*-Butyl)phenyl)-1-phenylmethanimine (3.61)**



To a solution of 2-*tert*-butylaniline (3.90 mL, 3.73 g, 25.0 mmol) in ethanol (100 mL) was added benzaldehyde (2.50 mL, 2.65 g, 25.0 mL) and the resulting solution was heated to reflux for 18 h. The reaction mixture was concentrated *in vacuo* to yield the title compound (5.93 g, 100%) as an orange oil that was used without further purification. δ_H (400 MHz, $CDCl_3$) 8.34 (1H, s, NCH), 7.96–7.90 (2H, m, ArH), 7.54–7.48 (3H, m, ArH), 7.42 (1H, dd, *J* = 7.5, 2.0 Hz, ArH), 7.27–7.16 (2H, m, ArH), 6.87 (1H, dd, *J* = 7.5, 2.0 Hz, ArH), 1.47 (9H, s, CH_3). Characterisation data matched those reported in the literature.[125]

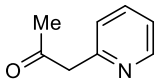
2-(*tert*-Butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline (3.55)



N,*N*-Diisopropylamine (7.00 mL, 5.06 g, 50.0 mmol) was dissolved in dry THF (120 mL) and cooled to –78 °C. *n*-BuLi (20.0 mL, 2.5 M in hexanes, 50.0 mmol) was added slowly and the resulting solution stirred for 15 minutes. 2-Methylpyridine (4.90 mL, 4.66 g, 50.0 mmol) was

added slowly and the resulting solution was stirred for 15 minutes. *N*-(2-(*tert*-butyl)phenyl)-1-phenylmethanimine **3.61** (5.93 g, 25.0 mmol) was dissolved in dry THF (25 mL) and added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (150 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 19:1 hexane:ethyl acetate) to yield the title compound (5.70 g, 69%) as an off-white solid. R_f 0.18 (19:1 hexane:ethyl acetate); m.p. 70–73 °C; δ_H (400 MHz, $CDCl_3$) 8.62–8.58 (1H, m, ArH), 7.53 (1H, td, *J* = 7.5, 2.0 Hz, ArH), 7.36–7.21 (6H, m, ArH), 7.19–7.13 (1H, m, ArH), 6.98–6.89 (2H, m, ArH), 6.62 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 6.36 (1H, dd, *J* = 8.5, 1.5 Hz, ArH), 5.61 (1H, d, *J* = 4.0 Hz, NH), 4.91 (1H, ddd, *J* = 8.0, 4.0, 4.0 Hz, NCH), 3.47 (1H, dd, *J* = 13.5, 4.0 Hz, C**H**H'), 3.25 (1H, dd, *J* = 13.5, 8.0 Hz, CH**H'**), 1.53 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 158.5 (ArC), 149.2 (ArC), 144.8 (ArC), 143.6 (ArC), 136.5 (ArC), 133.3 (ArC), 128.7 (ArC), 127.0 (ArC), 126.9 (ArC), 126.4 (ArC), 126.1 (ArC), 124.0 (ArC), 121.9 (ArC), 116.5 (ArC), 112.6 (ArC), 58.6 (NCH), 47.0 (CH_2), 34.4 (**C**$(CH_3)_3$), 29.8 (C(**C**$H_3)_3$); ν_{max}/cm^{-1} (thin film) 3422, 2956, 1593, 1577, 1510, 1474, 1446, 1311, 1273, 1055, 743, 701; HRMS (ESI); calcd. for $C_{23}H_{27}N_2^+$, 331.2169. Found: $[MH]^+$, 331.2181 (–3.6 ppm error).

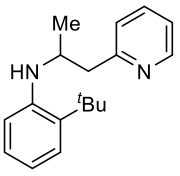
1-(Pyridin-2-yl)propan-2-one (3.64)



A solution of *N*,*N*-diisopropylamine (1.40 mL, 1.01 g, 10.0 mmol) was dissolved in dry THF (25 mL) and cooled to –78 °C before adding *n*-BuLi (4.00 mL, 2.5 M in hexane, 10.0 mmol) and stirring for 15 minutes. 2-Methylpyridine (0.490 mL, 466 mg, 5.00 mmol) was added dropwise and the mixture was stirred for 15 min. *N*-Methoxy-*N*-methylacetamide (1.10 mL, 1.03 g, 10.0 mmol) was added dropwise and the resulting mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with water (30 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, ethyl acetate) to yield the title compound (578 mg, 86%, 91:9 keto:enol) as a yellow oil. R_f 0.41 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.50–8.45 (1H, m, ArH, keto), 8.14–8.09 (1H, m, ArH, enol), 7.58 (1H, td, *J* = 7.5, 2.0 Hz, ArH, keto), 7.48–7.43

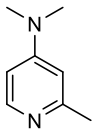
(1H, m, ArH, enol), 7.16–7.08 (2H, m, ArH, keto), 6.84–6.76 (2H, m, ArH, enol), 5.23 (1H, s, CH, enol), 3.85 (2H, s, CH_2, keto), 2.15 (3H, s, CH_3, keto), 1.95 (3H, s, CH_3, enol). Characterisation data matched those reported in the literature.[126]

2-(*tert*-Butyl)-*N*-(1-(pyridin-2-yl)propan-2-yl)aniline (3.65)



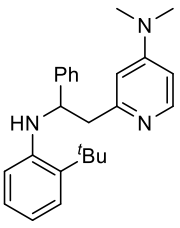
To a solution of 1-(pyridin-2-yl)propan-2-one **3.64** (513 mg, 3.80 mmol) in dry 1,2-dichloroethane (6.0 mL) was added 2-*tert*-butylaniline (0.540 mL, 515 mg, 3.45 mmol), acetic acid (0.220 mL, 228 mg, 3.80 mmol) and sodium triacetoxyborohydride (1.17 g, 5.52 mmol) and the mixture was stirred at 60 °C for 72 h. The reaction mixture was diluted with water (40 mL) and extracted with DCM (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 9:1 hexane:ethyl acetate) to yield the title compound (131 mg, 14%) as an orange oil. R_f 0.24 (9:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.60–8.56 (1H, m, ArH), 7.61 (1H, td, *J* = 7.5, 2.0 Hz, ArH), 7.26 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.23–7.19 (1H, m, ArH), 7.17–7.12 (2H, m, ArH), 6.78 (1H, d, *J* = 8.0 Hz, ArH), 6.67 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 4.57 (1H, s, NH), 4.15–4.04 (1H, m, NCH), 3.15 (1H, dd, *J* = 13.5, 6.0 Hz, C**H**H'), 3.06 (1H, dd, *J* = 13.5, 6.0 Hz, CH**H'**), 1.43 (9H, s, $C(CH_3)_3$), 1.27 (3H, d, *J* = 6.0 Hz, CH_3); δ_C (101 MHz, $CDCl_3$) 159.5 (ArC), 149.3 (ArC), 145.2 (ArC), 136.4 (ArC), 133.2 (ArC), 127.2 (ArC), 126.5 (ArC), 124.0 (ArC), 121.5 (ArC), 116.3 (ArC), 111.9 (ArC), 48.8 (NCH), 44.9 (CH_2), 34.2 (**C**$(CH_3)_3$), 29.9 (C(**C**$H_3)_3$), 20.2 (CH_3); ν_{max}/cm^{-1} (thin film) 3411, 1961, 1590, 1575, 1508, 1445, 1307, 1259, 1054, 995, 742; HRMS (ESI); calcd. for $C_{18}H_{25}N_2^+$, 269.2012. Found: $[MH]^+$, 269.2016 (–1.3 ppm error).

***N*,*N*,2-Trimethylpyridin-4-amine (3.66)**



To a solution of 4-bromo-2-methylpyridine (2.60 mL, 3.82 g, 22.2 mmol) in ethanol (33 mL) was added dimethylamine (100 mL, 2 M in methanol, 200 mmol) and the solution was heated to 75 °C for 7 days. The reaction mixture was concentrated *in vacuo* before adding water (150 mL) and extracting with DCM (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 94:5:1 ethyl acetate:methanol:triethylamine) to yield the title compound (2.16 g, 71%) as a yellow oil. R_f 0.27 (SiO_2, 94:5:1 ethyl acetate:methanol:triethylamine); δ_H (400 MHz, $CDCl_3$) 8.12 (1H, d, *J* = 6.0 Hz, ArH), 6.38–6.31 (2H, m, ArH), 2.98 (6H, s, NCH_3), 2.45 (3H, s, $ArCH_3$). Characterisation data matched those reported in the literature.[127]

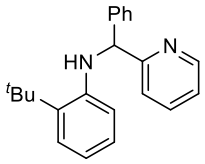
2-(2-((2-(*tert*-Butyl)phenyl)amino)-2-phenylethyl)-*N*,*N*-dimethylpyridin-4-amine (3.67)



N,*N*-Diisopropylamine (2.00 mL, 1.48 g, 14.6 mmol) was dissolved in dry THF (30 mL) and cooled to –78 °C. *n*-BuLi (5.80 mL, 2.5 M in hexanes, 14.6 mmol) was added slowly and the resulting solution stirred for 15 minutes. To this was added *N*,*N*,2-trimethylpyridin-4-amine **3.66** (1.99 g, 14.6 mmol), dissolved in THF (5 mL), dropwise and the resulting solution was stirred for 15 minutes. *N*-(2-(*tert*-butyl)phenyl)-1-phenylmethanimine **3.61** (1.73 g, 7.30 mmol) was dissolved in dry THF (7 mL) and added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 50:49:1 ethyl acetate:hexane:triethylamine) to yield the title compound (2.44 g, 89%) as an off-white

solid. R_f 0.30 (50:49:1 ethyl acetate:hexane:triethylamine); m.p. 38–43 °C; δ_H (400 MHz, $CDCl_3$) 8.21 (1H, d, *J* = 6.0 Hz, ArH), 7.41–7.36 (2H, m, ArH), 7.34–7.29 (2H, m, ArH), 7.26–7.20 (2H, m, ArH), 6.93–6.87 (1H, m, ArH), 6.60 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 6.39 (1H, dd, *J* = 6.0, 2.5 Hz, ArH), 6.35 (1H, dd, *J* = 8.5, 1.5 Hz, ArH), 6.14 (1H, d, *J* = 2.5 Hz, ArH), 5.60 (1H, d, *J* = 4.0 Hz, NH), 4.86 (1H, ddd, *J* = 8.0, 4.0, 4.0 Hz, NCH), 3.35 (1H, dd, *J* = 13.5, 4.0 Hz, C**H**H'), 3.09 (1H, dd, *J* = 13.5, 8.0 Hz, CH**H'**), 2.91 (6H, s, NCH_3), 1.52 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 158.1 (ArC), 154.8 (ArC), 149.3 (ArC), 145.0 (ArC), 144.1 (ArC), 133.3 (ArC), 128.6 (ArC), 126.8 (ArC), 126.5 (2 x ArC), 126.0 (ArC), 116.2 (ArC), 112.7 (ArC), 106.5 (ArC), 105.2 (ArC), 58.8 (NCH), 47.7 (CH_2), 39.1 (NCH_3), 34.4 ($\mathbf{C}(CH_3)_3$), 29.8 ($C(\mathbf{C}H_3)_3$); ν_{max}/cm^{-1} (thin film) 3380, 2953, 1599, 1576, 1548, 1509, 1446, 1375, 1276, 1224, 1056, 995, 909, 740, 700; HRMS (ESI); calcd. for $C_{25}H_{32}N_3^+$, 374.2591. Found: $[MH]^+$, 374.2592 (–0.3 ppm error).

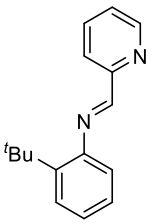
2-(*tert*-Butyl)-*N*-(phenyl(pyridin-2-yl)methyl)aniline (3.73)



2-Bromopyridine (7.90 g, 50.0 mmol) was dissolved in dry THF (120 mL) and cooled to –78 °C before adding *n*-BuLi (20 mL, 2.5 M in hexane, 50 mmol). The mixture was stirred for 15 minutes before adding *N*-(2-(*tert*-butyl)phenyl)-1-phenylmethanimine **3.61** (5.93 g, 25 mmol), dissolved in dry THF (20 mL), dropwise. The resulting mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (150 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 9:1 hexane:ethyl acetate) to yield the title compound (4.15 g, 52%) as a white solid. R_f 0.39 (9:1 hexane:ethyl acetate); m.p. 74–75 °C; δ_H (400 MHz, $CDCl_3$) 8.68–8.63 (1H, m, ArH), 7.64 (1H, td, *J* = 8.0, 2.0 Hz, ArH), 7.58–7.52 (2H, m, ArH), 7.43–7.24 (5H, m, ArH), 7.21–7.15 (1H, m, ArH), 7.04 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 6.71 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 6.59–6.54 (1H, m, ArH), 6.28 (1H, d, *J* = 4.0 Hz, NH), 5.70 (1H, d, *J* = 4.0 Hz, CH), 1.62 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 170.0 (ArC), 149.1 (ArC), 144.8 (ArC), 143.2 (ArC), 136.9 (ArC), 133.6 (ArC), 129.0 (ArC), 127.5 (ArC), 127.3 (ArC), 127.1 (ArC), 126.3 (ArC),

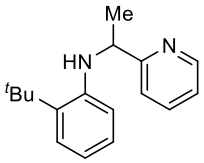
122.2 (ArC), 122.0 (ArC), 116.8 (ArC), 112.6 (ArC), 63.5 (CH), 34.4 (**C**$(CH_3)_3$), 30.0 (C(**C**$H_3)_3$); ν_{max}/cm^{-1} (thin film) 3438, 2957, 1595, 1573, 1504, 1447, 1428, 1309, 1262, 1055, 908, 741, 699, 591; HRMS (ESI); calcd. for $C_{22}H_{25}N_2^+$, 317.2012. Found: $[MH]^+$, 317.2016 (–1.1 ppm error).

_N_-(2-(_tert_-Butyl)phenyl)-1-(pyridin-2-yl)methanimine (3.75)



To a solution of 2-*tert*-butylaniline (1.56 mL, 1.49 g, 10.0 mmol) in ethanol (40 mL) was added 2-pyridinecarboxaldehyde (0.950 mL, 1.07 g, 10.0 mmol) and the solution was heated to reflux for 18 h. The reaction mixture was concentrated *in vacuo* to yield the crude product (2.38 g) which was used directly in the next step without further purification.

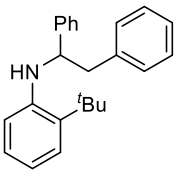
2-(_tert_-Butyl)-_N_-(1-(pyridin-2-yl)ethyl)aniline (3.76)



Methyllithium (12.5 mL, 1.6 M in Et_2O, 20.0 mmol) was diluted with THF (30 mL) and cooled to –78 °C. To this was added *N*-(2-(*tert*-butyl)phenyl)-1-(pyridin-2-yl)methanimine **3.75** (2.38 g, 10.0 mmol), dissolved in dry THF (10 mL), dropwise. The mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 9:1 hexane:ethyl acetate) to yield the title compound (2.31 g, 91%) as a yellow oil. R_f 0.30 (9:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.67–8.64 (1H, m, ArH), 7.64 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 7.42–7.38 (1H, m, ArH), 7.33 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.18 (1H, ddd, *J* = 7.5, 4.5, 1.0 Hz, ArH), 7.07 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 6.72 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 6.55 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 4.97 (1H, d, *J* = 5.5 Hz, NH), 4.82–4.73 (1H, m, CH), 1.67 (3H, d, *J* = 7.0 Hz, CH_3), 1.59 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$)

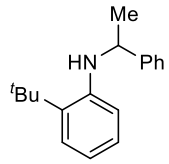
164.1 (ArC), 149.3 (ArC), 144.9 (ArC), 136.9 (ArC), 133.1 (ArC), 127.1 (ArC), 126.3 (ArC), 121.9 (ArC), 120.2 (ArC), 116.8 (ArC), 112.5 (ArC), 55.0 (CH), 34.2 (**C**(CH_3)$_3$), 30.0 (C(**C**H_3)$_3$), 23.5 (CH_3); ν_{max}/cm^{-1} (thin film) 3443, 2965, 1592, 1573, 1505, 1446, 1434, 1368, 1309, 1054, 781, 741; HRMS (ESI); calcd. for $C_{17}H_{23}N_2^+$, 255.1856. Found: $[MH]^+$, 255.1858 (–0.7 ppm error).

2-(*tert*-Butyl)-*N*-(1,2-diphenylethyl)aniline (3.77)



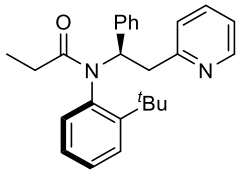
A solution of *N*-(2-(*tert*-butyl)phenyl)-1-phenylmethanimine **3.61** (942 mg, 3.97 mmol) in THF (17 mL) was cooled to –78 °C before adding benzylmagnesium chloride (4.00 mL, 2 M in THF, 8.00 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 19:1 hexane:ethyl acetate) to yield the title compound (1.25 g, 96%) as a yellow solid. R_f 0.61 (19:1 hexane:ethyl acetate); m.p. 66–69 °C; δ_H (400 MHz, $CDCl_3$) 7.37–7.13 (11H, m, ArH), 6.90–6.84 (1H, m, ArH), 6.61–6.55 (1H, m, ArH), 6.34 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 4.71 (1H, ddd, *J* = 9.0, 5.0, 3.5 Hz, NCH), 4.33 (1H, d, *J* = 3.5 Hz, NH), 3.26 (1H, dd, *J* = 14.0, 5.0 Hz, C**H**H'), 3.00 (1H, dd, *J* = 14.0, 9.0 Hz, CH**H'**), 1.28 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 145.0 (ArC), 144.0 (ArC), 137.7 (ArC), 133.4 (ArC), 129.5 (ArC), 128.8 (2 x ArC), 127.1 (2 x ArC), 126.9 (ArC), 126.5 (ArC), 126.1 (ArC), 117.0 (ArC), 113.1 (ArC), 59.3 (NCH), 45.9 (CH_2), 34.2 (**C**(CH_3)$_3$), 29.8 (C(**C**H_3)$_3$); ν_{max}/cm^{-1} (thin film) 3461, 3061, 2966, 1599, 1578, 1505, 1447, 1302, 1263, 1056, 742, 698; HRMS (ESI); calcd. for $C_{24}H_{28}N^+$, 330.2216. Found: $[MH]^+$, 330.2243 (–8.0 ppm error).

2-(*tert*-Butyl)-*N*-(1-phenylethyl)aniline (3.78)



Methyllithium (6.30 mL, 1.6 M in Et_2O, 10.0 mmol) was diluted with THF (20 mL) and cooled to –78 °C. To this was added *N*-(2-(*tert*-butyl)phenyl)-1-phenylmethanimine **3.61** (1.19 g, 5.00 mmol), dissolved in dry THF (5 mL), dropwise. The mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 19:1 hexane:ethyl acetate) to yield the title compound (1.18 g, 93%) as a yellow oil. R_f 0.68 (19:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.51–7.45 (2H, m, ArH), 7.44–7.39 (2H, m, ArH), 7.36–7.29 (2H, m, ArH), 7.08–7.01 (1H, m, ArH), 6.73 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 6.50 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 4.69–4.59 (1H, qd, *J* = 6.5, 4.5 Hz, NCH), 4.43 (1H, d, *J* = 4.0 Hz, NH), 1.68 (3H, d, *J* = 6.5 Hz, CH_3), 1.62 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 145.6 (ArC), 145.2 (ArC), 132.8 (ArC), 128.8 (ArC), 127.1 (ArC), 126.9 (ArC), 126.2 (ArC), 125.9 (ArC), 116.9 (ArC), 112.8 (ArC), 53.9 (NCH), 34.3 (**C**$(CH_3)_3$), 30.1 (C(**C**$H_3)_3$), 25.6 (CH_3); ν_{max}/cm^{-1} (thin film) 3487, 2963, 1599, 1578, 1506, 1446, 1370, 1306, 1261, 1205, 1055, 742, 699; HRMS (ESI); calcd. for $C_{18}H_{24}N^+$, 254.1903. Found: $[MH]^+$, 254.1911 (–3.2 ppm error).

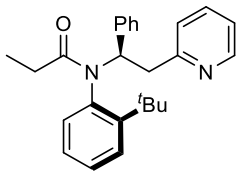
***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)propionamide (3.83)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added propionyl chloride (0.110 mL, 112 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and

concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 7:3 hexane:ethyl acetate) to yield the title compound (229 mg, 98%) as a colourless oil. R_f 0.17 (8:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.45–8.41 (1H, m, ArH), 7.61 (1H, dd, *J* = 8.5, 1.5 Hz, ArH), 7.45–7.32 (4H, m, ArH), 7.24–7.11 (4H, m, ArH), 7.03–6.93 (2H, m, ArH), 6.80 (1H, d, *J* = 8.0 Hz, ArH), 5.69 (1H, dd, *J* = 12.0, 4.5 Hz, NCH), 3.38 (1H, dd, *J* = 13.5, 4.5 Hz, ArC**H**H'), 2.93 (1H, dd, *J* = 13.5, 12.0 Hz, ArCH**H'**), 2.05–1.81 (2H, m, $COCH_2$), 1.41 (9H, s, $C(CH_3)_3$), 0.97 (3H, t, *J* = 7.5 Hz, CH_3); δ_C (101 MHz, $CDCl_3$) 174.2 (CO), 158.2 (ArC), 149.2 (ArC), 147.7 (ArC), 140.8 (ArC), 138.1 (ArC), 135.9 (ArC), 132.0 (ArC), 131.2 (ArC), 129.1 (ArC), 128.5 (ArC), 127.9 (ArC), 127.1 (ArC), 126.8 (ArC), 123.9 (ArC), 121.3 (ArC), 62.9 (NCH), 42.1 ($ArCH_2$), 36.7 (**C**$(CH_3)_3$), 32.9 (C(**C**$H_3)_3$), 30.0 (CO**C**H_2), 9.0 (CH_3); ν_{max}/cm^{-1} (thin film) 2970, 1656, 1590, 1570, 1487, 1436, 1478, 1263, 1147, 994, 836, 760, 748, 733, 700, 549; HRMS (ESI); calcd. for $C_{26}H_{31}N_2O^+$, 387.2431. Found: $[MH]^+$, 387.2436 (–1.4 ppm error).

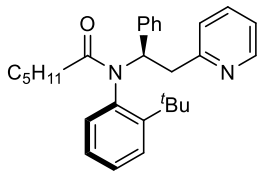
_N_-(2-(_tert_-Butyl)phenyl)-_N_-(1-phenyl-2-(pyridin-2-yl)ethyl)propionamide (3.84)



A solution of *N*-(2-(*tert*-butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)propionamide **3.83** (53 mg, 0.137 mmol) in d_6-DMSO (1.0 mL) was heated to 150 °C for 5 h. The reaction mixture was dissolved in DCM (10 mL) and washed with water (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 8:2 → 6:4 hexane:ethyl acetate) to yield the title compound (31 mg, 58%) as a colourless oil. R_f 0.16 (7:3 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.35–8.30 (1H, m, ArH), 7.45–7.29 (3H, m, ArH), 7.26–7.17 (2H, m, ArH), 7.13 (1H, d, *J* = 8.0 Hz, ArH), 7.07–6.92 (4H, m, ArH), 6.82–6.77 (2H, m, ArH), 5.88 (1H, dd, *J* = 10.5, 4.5 Hz, NCH), 3.79 (1H, dd, *J* = 13.0, 4.5 Hz, ArC**H**H'), 3.62 (1H, dd, *J* = 13.0, 10.5 Hz, ArC**H**H'), 2.03 (2H, q, *J* = 7.5 Hz, $COCH_2$), 1.06 (3H, t, *J* = 7.5 Hz, CH_3), 0.95 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 174.5 (CO), 158.6 (ArC), 148.9 (ArC), 147.8 (ArC), 137.8 (ArC), 137.4 (ArC), 136.0 (ArC), 132.0 (ArC), 131.1 (ArC), 130.9 (ArC), 128.6 (ArC), 127.8 (ArC), 127.7 (ArC), 126.7 (ArC), 124.0 (ArC), 121.2 (ArC), 63.9 (NCH), 44.4 ($ArCH_2$), 36.4 (**C**$(CH_3)_3$), 32.2

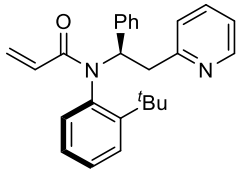
($C(\mathbf{C}H_3)_3$), 30.1 ($CO\mathbf{C}H_2$), 9.4 (CH_3); ν_{max}/cm^{-1} (thin film) 2954, 1650, 1591, 1569, 1489, 1435, 1388, 1248, 1077, 1052, 916, 760, 747, 731, 701; HRMS (ESI); calcd. for $C_{26}H_{30}N_2ONa^+$, 409.2250. Found: $[MNa]^+$, 409.2248 (0.6 ppm error).

_N_-(2-(_tert_-Butyl)phenyl)-_N_-(1-phenyl-2-(pyridin-2-yl)ethyl)hexanamide (3.89)



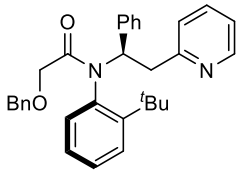
To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added hexanoyl chloride (0.250 mL, 245 mg, 1.82 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>96:4) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (250 mg, 96%) as a colourless oil. R_f 0.23 (8:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.43–8.38 (1H, m, ArH), 7.60 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.44–7.29 (4H, m, ArH), 7.23–7.09 (4H, m, ArH), 7.02 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 6.94 (1H, dd, *J* = 7.5, 5.0 Hz, ArH), 6.78 (1H, d, *J* = 8.0 Hz, ArH), 5.72 (1H, dd, *J* = 12.0, 4.5 Hz, NCH), 3.35 (1H, dd, *J* = 13.5, 4.5 Hz, ArC**H**H'), 2.92 (1H, dd, *J* = 13.5, 12.0 Hz, ArCH**H'**), 1.98–1.81 (2H, m, CH_2), 1.54–1.45 (2H, m, CH_2), 1.42 (9H, s, $C(CH_3)_3$), 1.20–0.99 (4H, m, 2 x CH_2), 0.77 (3H, t, *J* = 7.0 Hz, CH_3); δ_C (101 MHz, $CDCl_3$) 173.5 (CO), 158.2 (ArC), 149.2 (ArC), 147.7 (ArC), 140.8 (ArC), 138.1 (ArC), 135.9 (ArC), 132.1 (ArC), 131.2 (ArC), 129.1 (ArC), 128.5 (ArC), 127.9 (ArC), 127.1 (ArC), 126.7 (ArC), 123.9 (ArC), 121.2 (ArC), 62.7 (NCH), 42.1 ($ArCH_2$), 36.7 (CH_2, $\mathbf{C}(CH_3)_3$), 32.9 ($C(\mathbf{C}H_3)_3$), 31.5 (CH_2), 24.6 (CH_2), 22.4 (CH_2), 13.9 (CH_3); ν_{max}/cm^{-1} (thin film) 2956, 1653, 1590, 1569, 1486, 1436, 1383, 1262, 1218, 1091, 1051, 760, 699, 550; HRMS (ESI); calcd. for $C_{29}H_{37}N_2O^+$, 429.2900. Found: $[MH]^+$, 429.2903 (–0.7 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)acrylamide (3.90)**



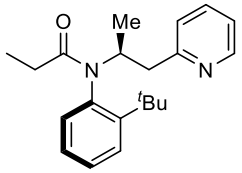
To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added acryloyl chloride (0.100 mL, 110 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. After 1 h the reaction was deemed incomplete by TLC and so acryloyl chloride (0.020 mL, 27 mg, 0.303 mmol) was added and the mixture stirred for a further 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>99:1) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 7:3 hexane:ethyl acetate) to yield the title compound (230 mg, 99%) as a colourless oil. R_f 0.32 (7:3 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.45–8.42 (1H, m, ArH), 7.62 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.48–7.42 (2H, m, ArH), 7.40–7.31 (2H, m, ArH), 7.24–7.11 (4H, m, ArH), 7.06 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 6.99–6.94 (1H, m, ArH), 6.81 (1H, d, *J* = 8.0 Hz, ArH), 6.32 (1H, dd, *J* = 17.0, 2.0 Hz, H'**H**C=CH), 5.88 (1H, dd, *J* = 17.0, 10.5 Hz, H'HC=C**H**), 5.78 (1H, dd, *J* = 12.0, 4.5 Hz, NCH), 5.42 (1H, dd, *J* = 10.5, 2.0 Hz, **H'**HC=CH), 3.40 (1H, dd, *J* = 13.5, 4.5 Hz, ArC**H**H'), 3.00 (1H, dd, *J* = 13.5, 12.0 Hz, ArCH**H'**), 1.39 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 166.1 (CO), 158.0 (ArC), 149.2 (ArC), 148.6 (ArC), 140.4 (ArC), 137.3 (ArC), 136.0 (ArC), 132.0 (ArC), 131.2 (ArC), 130.3 (H_2C=**C**H), 129.2 (ArC), 128.7 (ArC), 128.0 (ArC), 127.5 (H_2**C**=CH), 127.3 (ArC), 126.8 (ArC), 124.0 (ArC), 121.4 (ArC), 63.2 (NCH), 42.1 ($ArCH_2$), 36.7 (**C**(CH_3)$_3$), 32.9 (C(**C**H_3)$_3$); ν_{max}/cm^{-1} (thin film) 2961, 2242, 1655, 1616, 1591, 1487, 1436, 1406, 1336, 1262, 1076, 982, 910, 747, 729, 699, 579; HRMS (ESI); calcd. for $C_{26}H_{29}N_2O^+$, 385.2274. Found: $[MH]^+$, 385.2274 (0.2 ppm error).

2-(Benzyloxy)-*N*-(2-(*tert*-butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)acetamide (3.91)



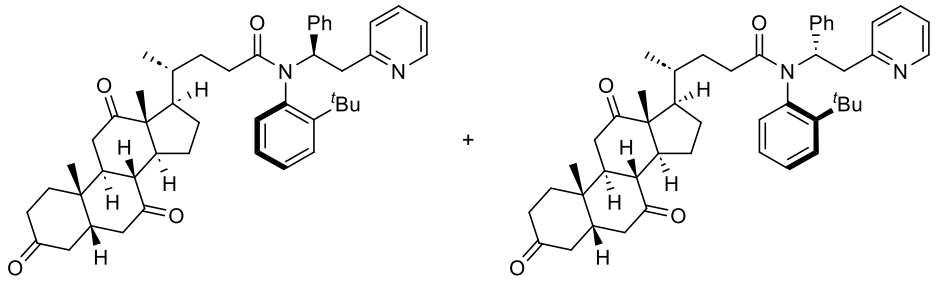
To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added benzyloxyacetyl chloride (223 mg, 1.21 mmol, prepared from benzyloxyacetic acid using the general procedure) and the resulting mixture was heated to 80 °C for 1 h. After this time the reaction was deemed incomplete by TLC and so benzyloxyacetyl chloride (112 mg, 0.605 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>90:10) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 6:4 hexane:ethyl acetate) to yield the title compound (202 mg, 70%) as a colourless oil. R_f 0.33 (6:4 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.47–8.40 (1H, m, ArH), 7.55 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.49–7.44 (2H, m, ArH), 7.38–7.30 (2H, m, ArH), 7.29–7.12 (9H, m, ArH), 6.97 (1H, dd, *J* = 7.5, 5.0 Hz, ArH), 6.89 (1H, dd, *J* = 8.0, 1.5 HZ, ArH), 6.83 (1H, d, *J* = 8.0 Hz, ArH), 5.72 (1H, dd, *J* = 12.0, 4.5 Hz, NCH), 4.60 (1H, d, *J* = 12.0 Hz, PhC**H**H'), 4.52 (1H, d, *J* = 12.0 Hz, PhCH**H'**), 3.71 (1H, d, *J* = 15.5 Hz, COC**H**H'), 3.61 (1H, d, *J* = 15.5 Hz, COCH**H'**), 3.43 (1H, dd, *J* = 13.5, 4.5 Hz, ArC**H**H'), 2.99 (1H, dd, *J* = 13.5, 12.0 Hz, ArCH**H'**), 1.33 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 169.7 (CO), 158.0 (ArC), 149.3 (ArC), 147.8 (ArC), 140.1 (ArC), 137.6 (ArC), 136.1 (ArC), 136.0 (ArC), 131.9 (ArC), 131.3 (ArC), 129.3 (ArC), 129.0 (ArC), 128.4 (ArC), 128.0 (2 x ArC), 127.7 (ArC), 127.4 (ArC), 126.9 (ArC), 124.0 (ArC), 121.4 (ArC), 72.9 ($PhCH_2$), 69.3 ($CO\mathbf{C}H_2$), 63.4 (NCH), 41.5 ($ArCH_2$), 36.6 ($\mathbf{C}(CH_3)_3$), 32.8 ($C(\mathbf{C}H_3)_3$); ν_{max}/cm^{-1} (thin film) 2958, 1735, 1719, 1670, 1590, 1474, 1395, 1277, 1198, 1115, 1028, 909, 728, 697; HRMS (ESI); calcd. for $C_{32}H_{35}N_2O_2^+$, 479.2693. Found: $[MH]^+$, 479.2698 (–0.9 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-(pyridin-2-yl)propan-2-yl)propionamide (3.92)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-(pyridin-2-yl)propan-2-yl)aniline **3.65** (127 mg, 0.473 mmol) and sodium bicarbonate (159 mg, 1.89 mmol) in dry acetonitrile (2.4 mL) was added propionyl chloride (0.080 mL, 88 mg, 0.946 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 7:3 hexane:ethyl acetate → 6:4 hexane:ethyl acetate) to yield the title compound (131 mg, 85%) as a yellow oil. R_f 0.24 (7:3 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.47–8.42 (1H, m, ArH), 7.58–7.50 (2H, m, ArH), 7.33–7.27 (1H, m, ArH), 7.20–7.11 (2H, m, ArH), 7.09–7.03 (1H, m, ArH), 6.99–6.95 (1H, m, ArH), 4.52 (1H, dqd, *J* = 12.5, 6.5, 3.5 Hz, NCH), 3.09 (1H, dd, *J* = 12.5, 3.5 Hz, ArC**H**H'), 2.52 (1H, dd, *J* = 12.5, 12.5 Hz, ArCH**H'**), 2.03–2.84 (2H, m, $COCH_2$), 1.40 (9H, s, $C(CH_3)_3$), 1.30 (3H, d, *J* = 6.5 Hz, CHC**H**$_3$), 1.01 (1H, t, *J* = 7.5 Hz, CH_2C**H**$_3$); δ_C (101 MHz, $CDCl_3$) 174.4 (CO), 159.2 (ArC), 149.3 (ArC), 146.9 (ArC), 138.6 (ArC), 136.4 (ArC), 131.3 (ArC), 130.7 (ArC), 128.5 (ArC), 127.0 (ArC), 123.8 (ArC), 121.5 (ArC), 55.4 (NCH), 42.6 ($ArCH_2$), 36.6 (**C**$(CH_3)_3$), 32.6 (C(**C**$H_3)_3$), 29.9 (CO**C**H_2), 18.7 (CH**C**H_3), 9.3 (CH_2**C**H_3); ν_{max}/cm^{-1} (thin film) 2970, 1650, 1590, 1569, 1487, 1436, 1375, 1267, 1240, 1050, 922, 760, 729, 574, 557; HRMS (ESI); calcd. for $C_{21}H_{29}N_2O^+$, 325.2274. Found: $[MH]^+$, 325.2277 (–0.8 ppm error).

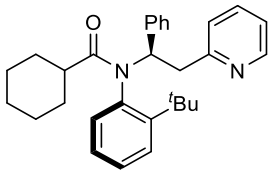
(4*R*)-*N*-(2-(*tert*-Butyl)phenyl)-4-((5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-3,7,12-trioxohexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)pentanamide (3.93)



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added dehydrocholic acid chloride (509 mg, 1.21 mmol, prepared from dehydrocholic acid using the general procedure) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography with respect to the atropisomeric amide portion. The crude product was then purified by column chromatography (SiO_2, 6:4 hexane:ethyl acetate) to yield the title compound (209 mg, 48%) as a 1:1 mixture of diastereoisomers and as a white solid. R_f 0.28 (6:4 hexane:ethyl acetate); m.p. 102–106 °C; δ_H (400 MHz, $CDCl_3$) 8.44–8.38 (2H, m, ArH, both diastereoisomers), 7.63–7.57 (2H, m, ArH, both diastereoisomers), 7.44–7.30 (8H, m, ArH), 7.24–7.09 (8H, m, ArH), 7.04–6.92 (4H, m, ArH), 6.81–6.76 (2H, m, ArH, both diastereoisomers), 5.70 (2H, dd, *J* = 12.0, 4.5 Hz, NCH, both diastereoisomers), 7.39–7.29 (2H, m, ArC**H**H', both diastereoisomers), 2.98–2.72 (8H, m, 6 x CH, ArCHH', both diastereoisomers), 2.37–1.50 (32H, m, CH), 1.41 (18H, s, $C(CH_3)_3$, both diastereoisomers), 1.37 (6H, s, CH_3, both diastereoisomers), 1.22–1.05 (8H, m, CH), 1.00–0.82 (8H, m, 2 x CH, CH_3, both diastereoisomers), 0.60–0.50 (6H, m, CH_3, both diastereoisomers); δ_C (101 MHz, $CDCl_3$) [Due to significant overlap of peaks of the different diastereoisomers, it was not possible to fully assign the peaks of both diastereoisomers.] 212.1 (2 x CO, both diastereoisomers), 209.2 (2 x CO, both diastereoisomers), 208.8 (2 x CO, both diastereoisomers), 173.8 (CO), 173.7 (CO), 158.2 (2 x ArC), 149.3 (ArC), 147.9 (ArC), 147.6 (ArC), 140.8 (ArC), 136.0 (ArC), 132.1 (ArC), 132.0 (ArC), 131.3 (ArC), 131.2 (ArC),

129.2 (2 x ArC), 128.6 (2 x ArC), 127.9 (2 x ArC), 127.2 (ArC), 127.1 (ArC), 126.8 (ArC), 126.7 (ArC), 124.0 (ArC), 123.9 (ArC), 121.3 (ArC), 62.7 (NCH, both diastereoisomers), 56.9 (C), 51.7 (C), 49.0 (C), 46.9 (C), 45.8 (C), 45.6 (C), 45.0 (C), 42.9 (C), 42.1 ($ArCH_2$), 38.7 (C), 36.7 (2 x C), 36.6 (C), 36.1 (C), 35.5 (C), 35.4 (C), 35.3 (C), 33.9 (2 x C), 33.0 ($C(\mathbf{C}H_3)_3$, both diastereoisomers), 30.7 (C), 30.6 (C), 27.5 (C), 25.2 (C), 22.0 (CH_3, both diastereoisomers), 19.0 (CH_3), 18.8 (CH_3), 11.9 (CH_3, both diastereoisomers); ν_{max}/cm^{-1} (thin film) 2961, 1707, 1647, 1591, 1487, 1435, 1385, 1273, 1051, 910, 727, 700, 646; HRMS (ESI); calcd. for $C_{47}H_{59}N_2O_4^+$, 715.4469. Found: $[MH]^+$, 715.4486 (–2.4 ppm error).

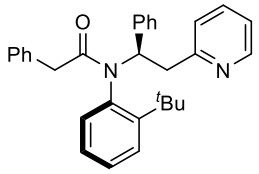
_N_-(2-(_tert_-Butyl)phenyl)-_N_-(1-phenyl-2-(pyridin-2-yl)ethyl)cyclohexanecarboxamide (3.94)



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added cyclohexanecarbonyl chloride (0.160 mL, 177 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 6:4 hexane:ethyl acetate) to yield the title compound (55 mg, 21%) as a white solid. R_f 0.16 (8:2 hexane:ethyl acetate); m.p. 119–124 °C; δ_H (400 MHz, $CDCl_3$) 8.44–8.39 (1H, m, ArH), 7.62 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.41–7.31 (4H, m, ArH), 7.23–7.09 (5H, m, ArH), 6.96 (1H, dd, *J* = 7.5, 5.0 Hz, ArH), 6.79 (1H, d, *J* = 8.0 Hz, ArH), 7.72 (1H, dd, *J* = 12.0, 4.5 Hz, NCH), 3.29 (1H, dd, *J* = 13.5, 4.5 Hz, ArC**H**H'), 2.90 (1H, dd, *J* = 13.5, 12.0 Hz, ArCH**H'**), 1.95 (1H, tt, *J* = 11.5, 3.0 Hz, COCH), 1.77–1.62 (3H, m, CHH'), 1.55–1.46 (3H, m, CHH'), 1.41 (9H, s, CH_3), 1.15–1.02 (2H, m, CHH'), 0.99–0.91 (1H, m, CHH'), 0.80–0.66 (1H, m, CHH'); δ_C (101 MHz, $CDCl_3$) 176.5 (CO), 158.3 (ArC), 149.3 (ArC), 147.8 (ArC), 141.1 (ArC), 137.7 (ArC), 135.9 (ArC), 131.9 (ArC), 131.1 (ArC), 128.9 (ArC), 128.5 (ArC), 127.9 (ArC), 127.1 (ArC), 126.5

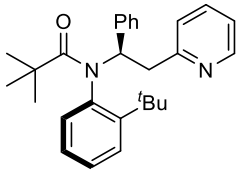
(ArC), 123.9 (ArC), 121.3 (ArC), 62.6 (NCH), 43.4 (CO**C**H), 42.4 ($ArCH_2$), 36.8 (**C**$(CH_3)_3$), 33.1 (C(**C**$H_3)_3$), 29.7 (CH_2), 27.9 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.3 (CH_2); ν_{max}/cm^{-1} (thin film) 2928, 1645, 1590, 1486, 1436, 1299, 1266, 1214, 1051, 909, 760, 728, 698; HRMS (ESI); calcd. for $C_{30}H_{37}N_2O^+$, 441.2900. Found: $[MH]^+$, 441.2904 (–0.8 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-2-phenyl-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)acetamide (3.95)**



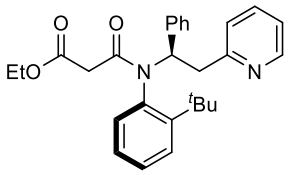
To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added phenylacetyl chloride (0.160 mL, 187 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 24 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^{1}H NMR spectrum of the crude product was taken to determine the *dr* (>98:2) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 7:3 hexane:ethyl acetate) to yield the title compound (29 mg, 11%) as a colourless oil. R_f 0.33 (7:3 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.45–8.40 (1H, m, ArH), 7.64 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.40–7.24 (5H, m, ArH), 7.20–7.28 (6H, m, ArH), 7.00–6.95 (1H, m, ArH), 6.94–6.89 (2H, m, ArH), 7.79–6.72 (2H, m, ArH), 5.65 (1H, dd, *J* = 11.5, 5.0 Hz, NCH), 3.46 (1H, dd, *J* = 13.0, 5.0 Hz, ArC**H**H'), 3.38 (1H, d, *J* = 15.0 Hz, COC**H**H'), 3.26 (1H, d, *J* = 15.0 Hz, COCH**H'**), 2.99 (1H, dd, *J* = 13.0, 11.5 Hz, ArCH**H'**), 1.45 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 171.4 (CO), 158.2 (ArC), 149.3 (ArC), 147.7 (ArC), 140.5 (ArC), 138.3 (ArC), 136.1 (ArC), 135.0 (ArC), 132.4 (ArC), 131.2 (ArC), 129.5 (ArC), 129.2 (ArC), 128.7 (ArC), 128.2 (ArC), 128.0 (ArC), 127.3 (ArC), 126.8 (ArC), 126.6 (ArC), 124.1 (ArC), 121.4 (ArC), 64.2 (NCH), 43.6 (CO**C**H_2), 42.2 ($ArCH_2$), 36.8 (**C**$(CH_3)_3$), 33.1 (C(**C**$H_3)_3$); ν_{max}/cm^{-1} (thin film) 2959, 1702, 1652, 1591, 1486, 1436, 1371, 1267, 1147, 910, 759, 730, 699, 548; HRMS (ESI); calcd. for $C_{31}H_{33}N_2O^+$, 449.2587. Found: $[MH]^+$, 449.2587 (0.1 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)pivalamide (3.96)**



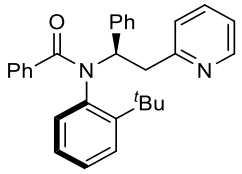
To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added pivaloyl chloride (0.150 mL, 146 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. No evidence of product formation was observed by TLC or ^{1}H NMR.

Ethyl 3-((2-(*tert*-butyl)phenyl)(1-phenyl-2-(pyridin-2-yl)ethyl)amino)-3-oxopropanoate (3.97)



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added ethyl malonyl chloride (0.150 mL, 182 mg, 1.21 mmol, prepared from mono-ethyl malonate using the general procedure) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. No evidence of product formation was observed by TLC or ^{1}H NMR.

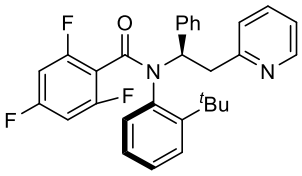
***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide (3.98)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added

benzoyl chloride (0.140 mL, 170 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>98:2) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 7:3 hexane:ethyl acetate) to yield the title compound (240 mg, 91%) as a white solid. In solution in $CDCl_3$, the product exists as a 95:5 mixture of rotamers (amide bond); full NMR data is given for the major rotamer only. R_f 0.40 (7:3 hexane:ethyl acetate); m.p. 119–123 °C; δ_H (400 MHz, $CDCl_3$) 8.53–8.48 (1H, m, ArH), 7.62–7.57 (2H, m, ArH), 7.44–7.38 (2H, m, ArH), 7.35–7.32 (1H, m, ArH), 7.30–7.11 (8H, m, ArH), 7.09–7.01 (3H, m, ArH), 6.95 (1H, d, *J* = 8.0 Hz, ArH), 5.99 (1H, dd, *J* = 11.0, 5.0 Hz, NCH), 3.54 (1H, dd, *J* = 13.5, 5.0 Hz, C**H**H'), 3.15 (1H, dd, *J* = 13.5, 11.0 Hz, CH**H'**), 1.08 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 169.8 (CO), 158.4 (ArC), 149.4 (ArC), 147.8 (ArC), 140.6 (ArC), 138.4 (ArC), 137.1 (ArC), 136.2 (ArC), 132.5 (ArC), 131.5 (ArC), 129.8 (ArC), 129.6 (ArC), 129.2 (ArC), 128.2 (2 x ArC), 127.5 (ArC), 127.3 (ArC), 126.1 (ArC), 124.2 (ArC), 121.6 (ArC), 64.8 (NCH), 42.0 (CH_2), 36.4 (**C**(CH_3)$_3$), 32.4 (C(**C**H_3)$_3$); ν_{max}/cm^{-1} (thin film) 2960, 1634, 1591, 1576, 1488, 1436, 1357, 1305, 1092, 1076, 910, 732, 717, 697; HRMS (ESI); calcd. for $C_{30}H_{31}N_2O^+$, 435.2431. Found: $[MH]^+$, 435.2423 (1.9 ppm error).

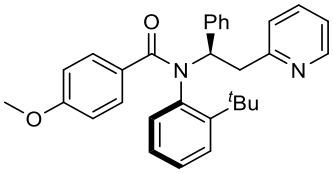
_N_-(2-(_tert_-Butyl)phenyl)-2,4,6-trifluoro-_N_-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide (3.99)



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 2,4,6-trifluorobenzoyl chloride (235 mg, 1.21 mmol, prepared from 2,4,6-trifluorobenzoic acid using the general procedure) and the resulting mixture was heated to 80 °C for 1 h. After this time the reaction was deemed incomplete by TLC and so 2,4,6-trifluorobenzoyl chloride (118 mg, 0.605 mmol) was added and the reaction mixture was stirred for a further

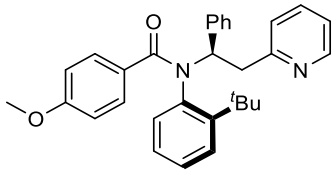
1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (253 mg, 86%) as a 74:26 mixture of rotamers and as a white solid. R_f 0.25 (8:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.46–8.42 (1H, m, ArH, major rotamer), 8.39–8.36 (1H, m, ArH, minor rotamer), 7.74–7.65 (2H, m, ArH), 7.53–7.14 (15H, m, ArH), 7.04–6.87 (3H, m, ArH), 6.83–6.78 (2H, m, ArH), 6.71–6.59 (2H, m, ArH), 6.54–6.44 (1H, m, ArH), 6.38–6.26 (2H, m, ArH), 6.20–6.12 (1H, m, ArH), 5.80 (1H, dd, *J* = 12.5, 4.0 Hz, NCH, major rotamer), 5.46 (1H, dd, *J* = 12.0, 4.0 Hz, NCH, minor rotamer), 3.29 (1H, dd, *J* = 12.5, 4.0 Hz, C**H**H', minor rotamer), 3.23 (1H, dd, *J* = 13.0, 4.0 Hz, C**H**H', major rotamer), 2.88 (1H, dd, *J* = 13.0, 12.5 Hz, CH**H'**, major rotamer), 2.59 (1H, dd, *J* = 12.5, 12.0 Hz, CH**H'**, minor rotamer), 1.63 (9H, s, CH_3, minor rotamer), 1.49 (9H, s, CH_3, major rotamer); δ_C (101 MHz, $CDCl_3$) [Due to the combination of the fluorine atoms causing peak splitting and the presence of rotamers, it was not possible to assign all peaks in the aromatic region. Peaks that could be identified have been listed.] 164.1 (CO), 163.9 (CO), 161.7 (ArC), 161.6 (ArC), 157.6 (ArC), 157.0 (ArC), 149.4 (ArC), 149.3 (ArC), 149.0 (ArC), 148.8 (ArC), 141.0 (ArC), 140.4 (ArC), 136.8 (ArC), 135.9 (ArC), 135.7 (ArC), 135.4 (ArC), 132.6 (ArC), 132.0 (ArC), 131.3 (ArC), 130.2 (ArC), 129.0 (ArC), 128.8 (ArC), 128.7 (ArC), 128.0 (ArC), 127.9 (ArC), 127.3 (ArC), 127.2 (ArC), 127.1 (ArC), 126.9 (ArC), 126.0 (ArC), 124.1 (ArC), 124.0 (ArC), 121.4 (ArC), 121.4 (ArC), 100.2 (ArC), 65.2 (NCH, minor rotamer), 64.7 (NCH, major rotamer), 45.1 (CH_2, minor rotamer), 43.0 (CH_2, major rotamer), 36.8 (**C**$(CH_3)_3$, major rotamer), 36.4 (**C**$(CH_3)_3$, minor rotamer), 32.8 (C(**C**$H_3)_3$, major rotamer), 32.2 (C(**C**$H_3)_3$, minor rotamer); δ_F (376 MHz, $CDCl_3$) –103.0 (1F, br m, ArF, major rotamer), –104.9 (1F, apparent t (broad), *J* = 8.5 Hz, ArF, minor rotamer), –105.0 (1F, br m, ArF, major rotamer), –105.7 (1F, apparent p (broad), *J* = 8.5 Hz, ArF, major rotamer), –106.3 (1F, apparent p (broad), *J* = 8.0 Hz, ArF, minor rotamer), –108.2 (1F, apparent t (broad), *J* = 8.5 Hz, ArF, minor rotamer); ν_{max}/cm^{-1} (thin film) 2963, 1651, 1638, 1599, 1488, 1437, 1365, 1302, 1120, 1036, 999, 910, 841, 728, 547; HRMS (ESI); calcd. for $C_{30}H_{28}F_3N_2O^+$, 489.2148. Found: $[MH]^+$, 489.2156 (–1.5 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-4-methoxy-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide (3.100a)**



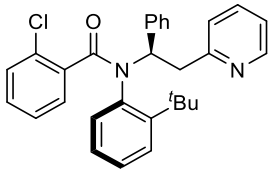
To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 4-methoxybenzoyl chloride (310 mg, 1.82 mmol) and the resulting mixture was heated to 80 °C for 2 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^{1}H NMR spectrum of the crude product was taken to determine the *dr* (97:3) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 6:4 hexane:ethyl acetate) to yield the title compound (213 mg, 76%) as a white solid. R_f 0.30 (6:4 hexane:ethyl acetate); m.p. 55–57 °C; δ_H (400 MHz, $CDCl_3$) 8.53–8.50 (1H, m, ArH), 7.60–7.54 (2H, m, ArH), 7.43–7.33 (3H, m, ArH), 7.29–7.13 (7H, m, ArH), 7.02 (1H, dd, *J* = 7.5, 5.0 Hz, ArH), 6.94 (1H, d, *J* = 8.0 Hz, ArH), 6.58–6.53 (2H, m, ArH), 5.98 (1H, dd, *J* = 11.0, 5.0 Hz, NCH), 3.67 (3H, s, OCH_3), 3.52 (1H, dd, *J* = 13.5, 5.0 Hz, C**H**H'), 3.14 (1H, dd, *J* = 13.5, 11.0 Hz, CH**H'**), 1.07 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 169.3 (CO), 130.4 (ArC), 158.5 (ArC), 149.4 (ArC), 147.8 (ArC), 140.7 (ArC), 138.7 (ArC), 136.1 (ArC), 132.3 (ArC), 131.7 (ArC), 131.5 (ArC), 129.4 (ArC), 129.1 (ArC), 128.1 (ArC), 128.0 (ArC), 127.3 (ArC), 126.1 (ArC), 124.2 (ArC), 121.5 (ArC), 112.5 (ArC), 64.7 (NCH), 55.2 (OCH_3), 42.0 (CH_2), 36.4 (**C**$(CH_3)_3$), 32.4 (C(**C**$H_3)_3$); ν_{max}/cm^{-1} (thin film) 2960, 1628, 1603, 1570, 1510, 1435, 1355, 1303, 1252, 1175, 1030, 909, 840, 763, 727, 699, 552; HRMS (ESI); calcd. for $C_{31}H_{33}N_2O_2^+$, 465.2537. Found: $[MH]^+$, 465.2546 (–1.9 ppm error).

_N_-(2-(_tert_-Butyl)phenyl)-4-methoxy-_N_-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide (3.101b)



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 4-methoxybenzoyl chloride (310 mg, 1.82 mmol) and the resulting mixture was heated to 80 °C for 24 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (83:17 **3.101a**:**3.101b**) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 6:4 hexane:ethyl acetate) to yield the title compound (47 mg, 17%) as a gummy white solid. R_f 0.05 (8:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.38 (1H, d, *J* = 5.0 Hz, ArH), 7.66–7.60 (1H, m, ArH), 7.52–7.45 (1H, m, ArH), 7.32–7.20 (6H, m, ArH), 7.08–6.90 (6H, m, ArH), 6.64–6.57 (2H, m, ArH), 6.26 (1H, dd, *J* = 10.0, 5.0 Hz, NCH), 3.97 (1H, dd, *J* = 13.0, 5.0 Hz, C**H**H'), 3.76–3.66 (4H, m, CH**H'**, OCH_3), 0.78 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 169.0 (CO), 160.3 (ArC), 158.6 (ArC), 148.9 (ArC), 147.9 (ArC), 137.6 (ArC), 137.2 (ArC), 136.2 (ArC), 133.4 (ArC), 131.5 (ArC), 131.4 (ArC), 131.2 (ArC), 129.6 (ArC), 128.4 (ArC), 127.8 (2 x ArC), 125.9 (ArC), 124.1 (ArC), 121.4 (ArC), 112.6 (ArC), 64.6 (NCH), 55.2 (OCH_3), 44.8 (CH_2), 36.3 (**C**$(CH_3)_3$), 32.1 (C(**C**$H_3)_3$); ν_{max}/cm^{-1} (thin film) 2957, 1730, 1626, 1605, 1510, 1489, 1435, 1339, 1304, 1252, 1176, 1031, 910, 840, 760, 729, 701, 610; HRMS (ESI); calcd. for $C_{31}H_{33}N_2O_2^+$, 465.2537. Found: $[MH]^+$, 465.2542 (–1.3 ppm error).

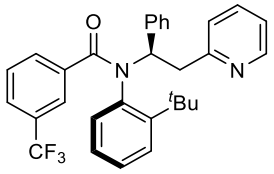
***N*-(2-(*tert*-Butyl)phenyl)-2-chloro-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide (3.102)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 2-chlorobenzoyl chloride (0.150 mL, 212 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 7:3 hexane:ethyl acetate) to yield the title compound (183 mg, 64%) as a 64:36 mixture of rotamers and as a white solid. R_f 0.27 (7:3 hexane:ethyl acetate); m.p. 42–46 °C; δ_H (400 MHz, $CDCl_3$) 8.47–8.43 (1H, m, ArH, major rotamer), 8.38 (1H, d, *J* = 4.5 Hz, ArH, minor rotamer), 7.70–7.54 (4H, m, ArH), 7.45–6.83 (25H, m, ArH), 6.76 (1H, d, *J* = 7.5 Hz, ArH, major rotamer), 6.66 (1H, d, *J* = 7.5 Hz, ArH, major rotamer), 6.31 (1H, d, *J* = 7.5 Hz, ArH, minor rotamer), 5.91 (1H, dd, *J* = 12.5, 4.0 Hz, NCH, major rotamer), 5.47 (1H, dd, *J* = 12.0, 4.0 Hz, NCH, minor rotamer), 3.40 (2H, m, C**H**H', both rotamers), 2.97 (1H, dd, *J* = 13.0, 12.5 Hz, CH**H'**, major rotamer), 2.68 (1H, dd, *J* = 12.5, 12.0 Hz, CH**H'**, minor rotamer), 1.69 (9H, s, CH_3, minor rotamer), 1.52 (9H, s, CH_3, major rotamer); δ_C (101 MHz, $CDCl_3$) 169.4 (CO, minor rotamer), 167.7 (CO, major rotamer), 157.8 (ArC), 157.2 (ArC), 149.4 (ArC), 149.2 (ArC), 148.3 (ArC), 148.1 (ArC), 139.9 (ArC), 139.6 (ArC), 137.0 (ArC), 136.7 (ArC), 136.6 (ArC), 136.3 (ArC), 135.9 (ArC), 135.8 (ArC), 132.9 (ArC), 132.8 (ArC), 131.9 (ArC), 131.6 (ArC), 131.1 (ArC), 130.4 (ArC), 130.3 (ArC), 129.9 (ArC), 129.8 (ArC), 129.5 (2 x ArC), 128.7 (ArC), 128.5 (ArC), 128.4 (ArC), 128.3 (ArC), 127.8 (2 x ArC), 127.4 (ArC), 127.2 (ArC), 126.7 (ArC), 126.4 (ArC), 126.1 (ArC), 125.7 (ArC), 125.5 (ArC), 124.1 (ArC), 123.9 (ArC), 121.4 (ArC), 121.2 (ArC), 65.5 (NCH, minor rotamer), 63.6 (NCH, major rotamer), 44.4 (CH_2, minor rotamer), 42.2 (CH_2, major rotamer), 37.1 (**C**$(CH_3)_3$, minor rotamer), 36.6 (**C**$(CH_3)_3$, major rotamer), 33.1 (C(**C**$H_3)_3$, major rotamer), 32.7 (C(**C**$H_3)_3$, minor rotamer); ν_{max}/cm^{-1} (thin film) 2962, 1643, 1591, 1487, 1473, 1434, 1361,

1304, 1153, 1041, 909, 727, 699, 644, 554; HRMS (ESI); calcd. for $C_{30}H_{30}{}^{35}ClN_2O^+$, 469.2041. Found: $[MH]^+$, 469.2029 (2.5 ppm error).

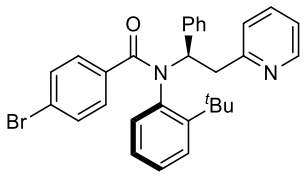
_N_-(2-(_tert_-Butyl)phenyl)-_N_-(1-phenyl-2-(pyridin-2-yl)ethyl)-3-(trifluoromethyl)benzamide (3.103)



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 3-(trifluoromethyl)benzoyl chloride (252 mg, 1.21 mmol, prepared from 3-(trifluoromethyl)benzoic acid using the general procedure) and the resulting mixture was heated to 80 °C for 1 h. After this time the reaction was deemed incomplete by TLC and so 3-(trifluoromethyl)benzoyl chloride (126 mg, 0.605 mmol) was added and the mixture stirred for a further 1 h. After this time the reaction was deemed incomplete by TLC and so 3-(trifluoromethyl)benzoyl chloride (126 mg, 0.605 mmol) was added and the mixture stirred for a further 1 h (3 h total reaction time). The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 6:4 hexane:ethyl acetate) to yield the title compound (234 mg, 77%) as a yellow oil. In solution in $CDCl_3$, the product exists as a 95:5 mixture of rotamers (amide bond); full NMR data is given for the major rotamer only. R_f 0.23 (8:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.59–8.53 (1H, m, ArH), 7.64–7.57 (2H, m, ArH), 7.49–7.16 (12H, m, ArH), 7.05 (1H, dd, *J* = 7.5, 5.0 Hz, ArH), 6.94 (1H, d, *J* = 8.0 Hz, ArH), 5.96 (1H, dd, *J* = 11.0, 5.5 Hz, NCH), 3.59 (1H, dd, *J* = 13.5, 5.5 Hz, C**H**H'), 3.21 (1H, dd, *J* = 13.5, 11.0 Hz, CH**H'**), 1.06 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 168.2 (CO), 158.0 (ArC), 149.2 (ArC), 147.7 (ArC), 140.1 (ArC), 137.9 (ArC), 137.7 (ArC), 136.4 (ArC), 133.0 (ArC), 132.2 (ArC), 131.7 (ArC), 129.7 (ArC, q, $^2J_{CF}$ = 32.6 Hz), 129.1 (ArC), 128.6 (ArC), 128.3 (ArC), 127.9 (ArC), 127.6 (ArC), 126.7 (ArC, q, $^3J_{CF}$ = 3.8 Hz), 126.4 (ArC), 126.1 (ArC, q, $^3J_{CF}$ = 3.4 Hz), 124.3 (ArC),

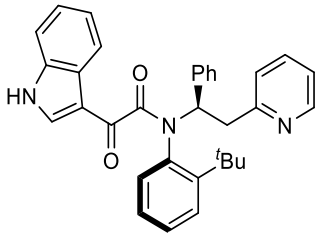
123.6 (CF_3, q, $^1J_{CF}$ = 274.7), 121.7 (ArC), 65.3 (NCH), 41.7 (CH_2), 36.3 (**C**$(CH_3)_3$), 32.4 (C(**C**$H_3)_3$); δ_F (376 MHz, $CDCl_3$) –62.8 (3F, s, CF_3); ν_{max}/cm^{-1} (thin film) 2963, 1636, 1590, 1488, 1436, 1325, 1301, 1278, 1168, 1127, 1073, 907, 728, 698, 554; HRMS (ESI); calcd. for $C_{31}H_{30}F_3N_2O^+$, 503.2305. Found: $[MH]^+$, 503.2310 (–1.0 ppm error).

4-Bromo-*N*-(2-(*tert*-butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide (3.104)



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 4-bromobenzoyl chloride (266 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^{1}H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (231 mg, 74%) as a white solid. In solution in $CDCl_3$, the product exists as a 95:5 mixture of rotamers (amide bond); full NMR data is given for the major rotamer only. R_f 0.26 (8:2 hexane:ethyl acetate); m.p. 49–53 °C; δ_H (400 MHz, $CDCl_3$) 8.55–8.50 (1H, m, ArH), 7.59–7.54 (2H, m, ArH), 7.44–7.34 (3H, m, ArH), 7.30–7.18 (7H, m, ArH), 7.10–7.01 (3H, m, ArH), 6.92 (1H, d, *J* = 7.5 Hz, ArH), 5.94 (1H, dd, *J* = 11.0, 5.5 Hz, NCH), 3.53 (1H, dd, *J* = 13.5, 5.5 Hz, C**H**H'), 3.13 (1H, dd, *J* = 13.5, 11.0 Hz, CH**H'**), 1.08 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 168.8 (CO), 158.3 (ArC), 149.5 (ArC), 147.9 (ArC), 140.4 (ArC), 138.2 (ArC), 136.2 (ArC), 136.0 (ArC), 132.3 (ArC), 131.7 (ArC), 131.4 (ArC), 130.6 (ArC), 129.1 (ArC), 128.4 (ArC), 128.3 (ArC), 127.6 (ArC), 126.3 (ArC), 124.2 (ArC), 124.1 (ArC), 121.6 (ArC), 65.1 (NCH), 42.0 (CH_2), 36.4 (**C**$(CH_3)_3$), 32.5 (C(**C**$H_3)_3$); ν_{max}/cm^{-1} (thin film) 2961, 1634, 1589, 1487, 1436, 1359, 1304, 1073, 1010, 909, 838, 751, 731, 705; HRMS (ESI); calcd. for $C_{30}H_{30}{}^{79}BrN_2O^+$, 513.1536. Found: $[MH]^+$, 513.1515 (4.0 ppm error).

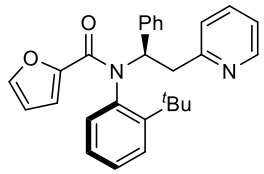
***N*-(2-(*tert*-Butyl)phenyl)-2-(1*H*-indol-3-yl)-2-oxo-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)acetamide (3.105)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 3-indoleglyoxylyl chloride (251 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^{1}H NMR spectrum of the crude product was taken to determine the *dr* (>97:3) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 6:4 hexane:ethyl acetate) to yield the title compound (265 mg, 87%) as a 67:37 mixture of rotamers and as a yellow solid. R_f 0.22 (6:4 hexane:ethyl acetate); m.p. 126–129 °C; δ_H (400 MHz, $CDCl_3$) 10.17–10.08 (2H, m, NH, both rotamers), 8.47–8.43 (1H, m, ArH, major rotamer), 8.33–8.29 (1H, m, ArH, minor rotamer), 8.13 (1H, d, *J* = 8.0 Hz, ArH, minor rotamer), 7.82–7.68 (2H, m, ArH), 7.56 (1H, dd, *J* = 8.0, 1.5 Hz, ArH, major rotamer), 7.50–7.83 (26H, m, ArH), 6.74 (1H, d, *J* = 8.0 Hz, ArH, major rotamer), 6.60–6.52 (2H, m, ArH), 6.42 (1H, t, *J* = 7.5 Hz, ArH, minor rotamer), 5.93–5.83 (2H, m, NCH, both rotamers), 3.36 (1H, dd, *J* = 13.0, 4.0 Hz, C**H**H', major rotamer), 3.16 (1H, dd, *J* = 12.5, 4.0 Hz, C**H**H', minor rotamer), 2.83 (1H, dd, *J* = 13.0, 13.0 Hz, CH**H'**, major rotamer), 2.71 (1H, dd, *J* = 12.5, 12.5 Hz, CH**H'**, minor rotamer), 1.65–1.59 (18H, m, CH_3, both rotamers); δ_C (101 MHz, $CDCl_3$) 185.2 (CO, minor rotamer), 184.6 (CO, major rotamer), 169.1 (CO, minor rotamer), 167.7 (CO, major rotamer), 157.4 (ArC), 157.1 (ArC), 149.6 (ArC), 149.3 (ArC), 149.1 (ArC), 149.0 (ArC), 140.4 (ArC), 139.8 (ArC), 136.4 (ArC), 136.2 (ArC), 136.0 (2 x ArC), 134.7 (ArC), 134.6 (ArC), 132.2 (ArC), 132.1 (ArC), 131.3 (ArC), 130.1 (ArC), 129.3 (ArC), 129.2 (ArC), 129.1 (ArC), 128.9 (ArC), 128.1 (ArC), 127.7 (ArC), 126.9 (ArC), 126.1 (ArC), 125.7 (ArC), 125.1 (ArC), 124.1 (ArC), 123.9 (ArC), 123.5 (ArC), 123.4 (ArC), 122.6 (ArC), 122.5 (ArC), 121.7 (ArC), 121.6 (ArC), 121.5 (ArC), 114.8 (ArC), 113.6 (ArC),

112.0 (ArC), 111.9 (ArC), 64.7 (NCH, minor rotamer), 62.7 (NCH, major rotamer), 44.7 (CH_2, minor rotamer), 41.4 (CH_2, major rotamer), 37.2 (**C**$(CH_3)_3$, major rotamer), 36.8 (**C**$(CH_3)_3$, minor rotamer), 32.9 (C(**C**$H_3)_3$major rotamer), 32.3 (C(**C**$H_3)_3$), minor rotamer); ν_{max}/cm^{-1} (thin film) 3242, 2961, 1617, 1595, 1517, 1487, 1436, 1406, 1352, 1300, 1244, 1154, 1134, 1032, 908, 749, 729, 705; HRMS (ESI); calcd. for $C_{33}H_{32}N_3O_2^+$, 502.2489. Found: $[MH]^+$, 502.2504 (–3.1 ppm error).

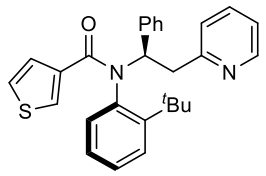
***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)furan-2-carboxamide (3.106)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 2-furoyl chloride (0.120 mL, 158 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. After 1 hour the reaction was deemed incomplete by TLC and so additional 2-furoyl chloride (0.060 mL, 79 mg, 0.605 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^{1}H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (216 mg, 84%) as a white solid. R_f 0.11 (8:2 hexane:ethyl acetate); m.p. 130–134 °C; δ_H (400 MHz, $CDCl_3$) 8.45–8.40 (1H, m, ArH), 7.57–7.47 (3H, m, ArH), 7.41–7.27 (3H, m, ArH), 7.26–7.08 (5H, m, ArH), 6.97–6.91 (1H, m, ArH), 6.85 (1H, d, *J* = 8.0 Hz, ArH), 6.06 (1H, dd, *J* = 3.5, 2.0 Hz, ArH), 5.92 (1H, dd, *J* = 11.5, 4.5 Hz, NCH), 5.19 (1H, d, *J* = 3.5 Hz, ArH), 3.44 (1H, dd, *J* = 13.5, 4.5 Hz, C**H**H'), 3.09 (1H, dd, *J* = 13.5, 11.5 Hz, CH**H'**), 1.20 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 159.6 (CO), 158.0 (ArC), 149.3 (ArC), 148.5 (ArC), 147.9 (ArC), 144.4 (ArC), 140.0 (ArC), 137.6 (ArC), 136.0 (ArC), 132.3 (ArC), 131.4 (ArC), 129.3 (ArC), 128.9 (ArC), 128.0 (ArC), 127.4 (ArC), 126.7 (ArC), 124.0 (ArC), 121.4 (ArC), 116.1 (ArC), 110.9 (ArC), 63.6 (NCH), 41.6 (CH_2), 36.6 (**C**$(CH_3)_3$), 32.7 (C(**C**$H_3)_3$); ν_{max}/cm^{-1} (thin film) 2961, 2243,

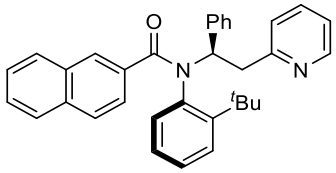
1634, 1591, 1470, 1436, 1394, 1354, 1305, 1183, 1140, 1092, 1012, 911, 699, 756, 726, 557; HRMS (ESI); calcd. for $C_{28}H_{29}N_2O_2^+$, 425.2224. Found: $[MH]^+$, 425.2214 (2.3 ppm error).

_N_-(2-(_tert_-Butyl)phenyl)-_N_-(1-phenyl-2-(pyridin-2-yl)ethyl)thiophene-3-carboxamide (3.107)



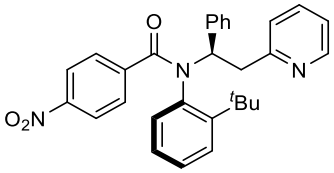
To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added thiophene-3-carbonyl chloride (177 mg, 1.21 mmol, prepared from thiophene-3-carboxylic acid using the general procedure) and the resulting mixture was heated to 80 °C for 2 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 7:3 hexane:ethyl acetate) to yield the title compound (175 mg, 66%) as a white solid. R_f 0.17 (8:2 hexane:ethyl acetate); m.p. 98–100 °C; δ_H (400 MHz, $CDCl_3$) 8.50–8.46 (1H, m, ArH), 7.57–7.48 (3H, m, ArH), 7.42–7.32 (3H, m, ArH), 7.31–7.13 (4H, m, ArH), 7.03–6.95 (3H, m, ArH), 6.89 (1H, d, *J* = 8.0 Hz, ArH), 6.69–6.66 (1H, m, ArH), 5.87 (1H, dd, *J* = 11.5, 4.5 Hz, NCH), 3.45 (1H, dd, *J* = 13.5, 4.5 Hz, C**H**H'), 3.11 (1H, dd, *J* = 13.5, 11.5 Hz, CH**H'**), 1.15 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 164.2 (CO), 158.3 (ArC), 149.4 (ArC), 148.5 (ArC), 140.6 (ArC), 138.4 (ArC), 138.2 (ArC), 136.1 (ArC), 132.3 (ArC), 131.8 (ArC), 130.2 (ArC), 130.0 (ArC), 129.2 (ArC), 128.8 (ArC), 128.1 (ArC), 127.4 (ArC), 126.6 (ArC), 124.0 (ArC), 123.8 (ArC), 121.5 (ArC), 64.0 (NCH), 42.0 (CH_2), 36.6 (**C**$(CH_3)_3$), 32.6 (C(**C**$H_3)_3$); ν_{max}/cm^{-1} (thin film) 2962, 1623, 1592, 1487, 1436, 1417, 1335, 1296, 1077, 906, 726, 698, 645, 554; HRMS (ESI); calcd. for $C_{28}H_{29}N_2OS^+$, 441.1995. Found: $[MH]^+$, 441.2003 (–1.7 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)-2-naphthamide (3.108)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 2-naphthoyl chloride (231 mg, 1.21 mmol, prepared from 2-napthoic acid using the general procedure) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 7:3 hexane:ethyl acetate) to yield the title compound (191 mg, 65%) as a white solid. R_f 0.15 (8:2 hexane:ethyl acetate); m.p. 63–66 °C; δ_H (400 MHz, $CDCl_3$) 8.58–8.53 (1H, m, ArH), 7.70–7.61 (4H, m, ArH), 7.59–7.51 (3H, m, ArH), 7.45–7.20 (10H, m, ArH), 7.07–7.02 (1H, m, ArH), 6.98 (1H, d, *J* = 7.5 Hz, ArH), 6.06 (1H, dd, *J* = 11.0, 5.5 Hz, NCH), 3.61 (1H, dd, *J* = 13.5, 5.5 Hz, C**H**H'), 3.22 (1H, dd, *J* = 13.5, 11.5 Hz, CH**H'**), 1.07 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$), 169.7 (CO), 158.4 (ArC), 149.4 (ArC), 147.9 (ArC), 140.6 (ArC), 138.5 (ArC), 136.2 (ArC), 134.2 (ArC), 133.4 (ArC), 132.5 (ArC), 132.0 (ArC), 131.6 (ArC), 130.4 (ArC), 129.2 (ArC), 128.8 (ArC), 128.2 (2 x ArC), 127.5 (ArC), 127.4 (ArC), 127.2 (ArC), 126.9 (ArC), 126.6 (ArC), 126.1 (2 x ArC), 124.3 (ArC), 121.6 (ArC), 64.9 (NCH), 42.0 (CH_2), 36.4 (**C**(CH_3)$_3$), 32.5 (C(**C**H_3)$_3$); v_{max}/cm^{-1} (thin film) 2962, 1635, 1624, 1592, 1487, 1435, 1386, 1303, 1200, 1089, 907, 758, 726, 699, 476; HRMS (ESI); calcd. for $C_{34}H_{33}N_2O^+$, 485.2587. Found: $[MH]^+$, 485.2563 (5.1 ppm error).

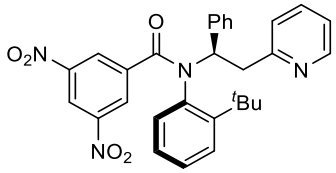
***N*-(2-(*tert*-Butyl)phenyl)-4-nitro-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide (3.109)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 4-nitrobenzoyl chloride (225 mg, 1.21 mmol, prepared from 4-nitrobenzoic acid using the general procedure) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 6:4 hexane:ethyl acetate) to yield the title compound (143 mg, 49%) as a white solid. In solution in $CDCl_3$, the product exists as a 94:6 mixture of rotamers (amide bond); full NMR data is given for the major rotamer only. R_f 0.38 (6:4 hexane:ethyl acetate); m.p. 48–50 °C; δ_H (400 MHz, $CDCl_3$) 8.56–8.52 (1H, m, ArH), 7.95–7.90 (2H, m, ArH), 7.60–7.54 (2H, m, ArH), 7.46–7.33 (5H, m, ArH), 7.30–7.19 (5H, m, ArH), 7.07–7.02 (1H, m, ArH), 6.90 (1H, d, *J* = 8.0 Hz, ArH), 5.94 (1H, dd, *J* = 11.0, 5.5 Hz, NCH), 3.54 (1H, dd, *J* = 13.5, 5.5 Hz, C**H**H'), 3.14 (1H, dd, *J* = 13.5, 11.0 Hz, CH**H'**), 1.10 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 167.7 (CO), 158.0 (ArC), 149.5 (ArC), 148.0 (ArC), 147.7 (ArC), 143.1 (ArC), 140.0 (ArC), 137.5 (ArC), 136.2 (ArC), 132.3 (ArC), 131.8 (ArC), 130.6 (ArC), 129.1 (ArC), 128.9 (ArC), 128.3 (ArC), 127.8 (ArC), 126.5 (ArC), 124.2 (ArC), 122.5 (ArC), 121.7 (ArC), 65.3 (NCH), 41.9 (CH_2), 36.4 (**C**(CH_3)$_3$), 32.6 (C(**C**H_3)$_3$); v_{max}/cm^{-1} (thin film) 2961, 1637, 1595, 1521, 1487, 1436, 1343, 1305, 1092, 1051, 908, 864, 723, 699, 557; HRMS (ESI); calcd. for $C_{30}H_{30}N_3O_3^+$, 480.2282. Found: $[MH]^+$, 480.2261 (4.2 ppm error).

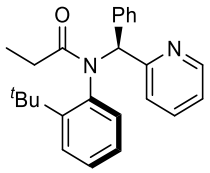
Characteristic data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 8.46–8.42 (1H, m, ArH), 5.65 (1H, dd, *J* = 11.5, 4.0 Hz, NCH), 2.64 (1H, dd, *J* = 13.0, 11.5 Hz, C**H**H').

***N*-(2-(*tert*-Butyl)phenyl)-3,5-dinitro-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide (3.110)**



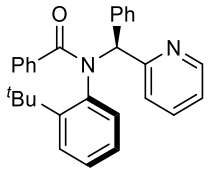
To a mixture of 2-(*tert*-butyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)aniline **3.55** (200 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 3,5-dinitrobenzoyl chloride (279 mg, 1.21 mmol, prepared from 3,5-dintrobenzoic acid using the general procedure) and the resulting mixture was heated to 80 °C for 24 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (21 mg, 7%) as a yellow oil. R_f 0.24 (8:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.84 (1H, t, *J* = 2.0 Hz, ArH), 8.59–8.56 (1H, m, ArH), 8.36 (2H, d, *J* = 2.0 Hz, ArH), 7.60–7.55 (2H, m, ArH), 7.53–7.49 (1H, m, ArH), 7.46–7.23 (7H, m, ArH), 7.11–7.06 (1H, m, ArH), 6.90 (1H, d, *J* = 8.0 Hz, ArH), 5.90 (1H, dd, *J* = 10.5, 5.5 Hz, NCH), 3.61 (1H, dd, *J* = 13.5, 5.5 Hz, C**H**H'), 3.19 (1H, dd, *J* = 13.5, 10.5 Hz, CH**H'**), 1.10 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 164.9 (CO), 157.7 (ArC), 149.7 (ArC), 147.9 (ArC), 147.6 (ArC), 140.5 (ArC), 139.5 (ArC), 137.2 (ArC), 136.4 (ArC), 132.1 (ArC), 131.9 (ArC), 129.7 (ArC), 129.6 (ArC), 129.2 (ArC), 128.5 (ArC), 128.1 (ArC), 127.4 (ArC), 124.3 (ArC), 121.9 (ArC), 119.4 (ArC), 66.3 (NCH), 41.9 (CH_2), 36.5 (**C**$(CH_3)_3$), 32.7 (C(**C**$H_3)_3$); v_{max}/cm^{-1} (thin film) 2961, 1644, 1590, 1541, 1436, 1341, 1305, 1077, 911, 764, 728, 700; HRMS (ESI); calcd. for $C_{30}H_{29}N_4O_5^+$, 525.2132. Found: $[MH]^+$, 525.2140 (–1.4 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-*N*-(phenyl(pyridin-2-yl)methyl)propionamide (3.112)**



To a mixture of 2-(*tert*-butyl)-*N*-(phenyl(pyridin-2-yl)methyl)aniline **3.73** (191 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added propionyl chloride (0.110 mL, 112 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (176 mg, 78%) as a white solid. R_f 0.30 (8:2 hexane:ethyl acetate); m.p. 133–136 °C; δ_H (400 MHz, $CDCl_3$) 8.51–8.47 (1H, m, ArH), 7.59 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.47–7.21 (8H, m, ArH), 7.19–7.13 (1H, m, ArH), 7.07–7.01 (1H, m, ArH), 6.83–6.77 (1H, m, ArH), 6.60 (1H, s, CH), 2.11 (2H, qd, *J* = 7.5, 2.5 Hz, CH_2), 1.15–1.05 (12H, m, $C(CH_3)_3$, CH_3); δ_C (101 MHz, $CDCl_3$) 174.9 (CO), 159.0 (ArC), 148.6 (ArC), 147.5 (ArC), 140.5 (ArC), 139.7 (ArC), 135.7 (ArC), 132.3 (ArC), 130.7 (ArC), 129.0 (ArC), 128.4 (ArC), 128.3 (ArC), 127.2 (ArC), 126.7 (ArC), 126.0 (ArC), 122.2 (ArC), 70.5 (CH), 36.4 (**C**$(CH_3)_3$), 32.4 ($C($**C**$H_3)_3$), 30.0 (CH_2), 9.3 (CH_3); ν_{max}/cm^{-1} (thin film) 2969, 1659, 1588, 1570, 1488, 1434, 1378, 1247, 1077, 910, 749, 730, 700, 614; HRMS (ESI); calcd. for $C_{25}H_{29}N_2O^+$, 373.2274. Found: $[MH]^+$, 373.2288 (–3.7 ppm error).

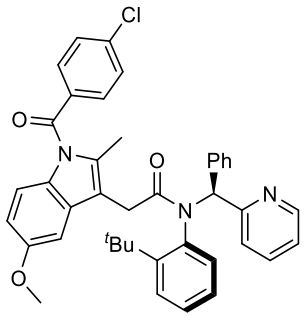
***N*-(2-(*tert*-Butyl)phenyl)-*N*-(phenyl(pyridin-2-yl)methyl)benzamide (3.113)**



To a mixture of 2-(*tert*-butyl)-*N*-(phenyl(pyridin-2-yl)methyl)aniline **3.73** (191 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added benzoyl chloride (0.140 mL, 170 mg, 1.21 mmol) and the resulting mixture was heated to

80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (178 mg, 70%) as a white solid. R_f 0.35 (8:2 hexane:ethyl acetate); m.p. 114–117 °C; δ_H (400 MHz, $CDCl_3$) 8.51–8.46 (1H, m, ArH), 7.76–7.71 (1H, m, ArH), 7.60–7.56 (2H, m, ArH), 7.43–7.36 (5H, m, ArH), 7.35–7.29 (1H, m, ArH), 7.23–7.17 (1H, m, ArH), 7.16–7.07 (5H, m, ArH), 7.05–7.00 (2H, m, ArH, NCH), 6.96–6.91 (1H, m, ArH), 0.91 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 169.7 (CO), 158.7 (ArC), 148.8 (ArC), 147.6 (ArC), 140.2 (ArC), 138.7 (ArC), 136.8 (ArC), 135.6 (ArC), 132.7 (ArC), 131.2 (ArC), 130.1 (ArC), 129.7 (ArC), 128.8 (ArC), 128.6 (ArC), 127.8 (ArC), 127.4 (2 x ArC), 126.4 (ArC), 125.6 (ArC), 122.2 (ArC), 71.0 (NCH), 36.3 (**C**$(CH_3)_3$), 32.1 (C(**C**$H_3)_3$); ν_{max}/cm^{-1} (thin film) 2960, 1636, 1588, 1572, 1489, 1434, 1342, 1094 1029, 910, 760, 729, 697, 610; HRMS (ESI); calcd. for $C_{29}H_{29}N_2O^+$, 421.2274. Found: $[MH]^+$, 421.2287 (–3.1 ppm error).

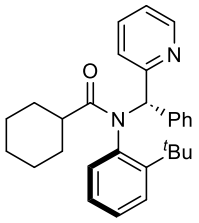
_N_-(2-(_tert_-Butyl)phenyl)-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1_H_-indol-3-yl)-_N_-(phenyl(pyridin-2-yl)methyl)acetamide (3.114)



To a mixture of 2-(*tert*-butyl)-*N*-(phenyl(pyridin-2-yl)methyl)aniline **3.73** (191 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl chloride (455 mg, 1.21 mmol, prepared from indomethacin using the general procedure) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude

product was then purified by column chromatography (SiO_2, 79:20:1: hexane:ethyl acetate:triethylamine) to yield the title compound (321 mg, 88%) as a yellow solid. R_f 0.52 (7:3 hexane:ethyl acetate); m.p. 74–79 °C; δ_H (400 MHz, $CDCl_3$) 8.46–8.43 (1H, m, ArH), 7.67–7.58 (3H, m, ArH), 7.49–7.43 (3H, m, ArH), 7.39–7.18 (7H, m, ArH), 7.15 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 7.05–6.99 (2H, m, ArH), 6.87 (1H, d, *J* = 9.0 Hz, ArH), 6.72 (1H, d, *J* = 8.0 Hz, ArH), 6.66 (1H, dd, *J* = 9.0, 2.5 Hz, ArH), 6.56 (1H, s, NCH), 3.73 (3H, s, OCH_3), 3.64 (1H, d, *J* = 15.5 Hz, C**H**H'), 3.46 (1H, d, *J* = 15.5 Hz, CH**H'**), 1.92 (3H, s, $ArCH_3$), 1.27 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 170.7 (CO), 168.4 (CO), 158.7 (ArC), 155.9 (ArC), 148.6 (ArC), 147.7 (ArC), 140.0 (ArC), 139.3 (ArC), 139.1 (ArC), 135.9 (ArC), 135.8 (ArC), 134.3 (ArC), 132.7 (ArC), 131.3 (ArC), 131.2 (ArC), 131.1 (ArC), 130.9 (ArC), 129.1 (2 x ArC), 128.6 (ArC), 128.4 (ArC), 127.4 (ArC), 126.9 (ArC), 125.8 (ArC), 122.2 (ArC), 114.8 (ArC), 113.6 (ArC), 111.8 (ArC), 102.2 (ArC), 71.6 (NCH), 55.6 (OCH_3), 36.6 (**C**$(CH_3)_3$), 33.7 (CH_2), 32.7 (C(**C**$H_3)_3$), 13.1 ($ArCH_3$); ν_{max}/cm^{-1} (thin film) 2959, 1666, 1589, 1475, 1434, 1361, 1316, 1223, 1147, 1088, 909, 754, 727, 701; HRMS (ESI); calcd. for $C_{41}H_{39}{}^{35}ClN_3O_3^+$, 656.2674. Found: $[MH]^+$, 656.2695 (–3.2 ppm error).

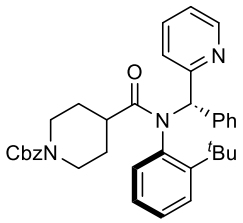
***N*-(2-(*tert*-Butyl)phenyl)-*N*-(phenyl(pyridin-2-yl)methyl)cyclohexanecarboxamide (3.115)**



To a mixture of 2-(*tert*-butyl)-*N*-(phenyl(pyridin-2-yl)methyl)aniline **3.73** (191 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added cyclohexanecarbonyl chloride (0.160 mL, 177 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 89:10:1 hexane:ethyl acetate:triethylamine → 79:20:1 hexane:ethyl acetate:triethylamine) to yield the title compound (197 mg, 76%) as a yellow oil. R_f 0.19 (89:10:1 hexane:ethyl

acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 8.49–8.45 (1H, m, ArH), 7.59 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.45–7.19 (8H, m, ArH), 7.15–7.09 (1H, m, ArH), 7.04–6.99 (1H, m, ArH), 6.77 (1H, d, *J* = 8.0 Hz, ArH), 6.64 (1H, s, NCH), 2.15 (1H, tt, *J* = 11.5, 3.5 Hz, COCH), 1.98–1.89 (1H, m, CHH'), 1.82–1.49 (5H, m, CHH'), 1.39–0.75 (13H, $C(CH_3)_3$, CHH'); δ_C (101 MHz, $CDCl_3$) 176.8 (CO), 158.9 (ArC), 148.5 (ArC), 147.4 (ArC), 140.6 (ArC), 138.8 (ArC), 135.6 (ArC), 132.2 (ArC), 130.6 (ArC), 128.7 (ArC), 128.3 (ArC), 128.1 (ArC), 127.1 (ArC), 126.3 (ArC), 126.0 (ArC), 122.1 (ArC), 69.9 (NCH), 43.1 (CO**C**H), 36.5 (**C**$(CH_3)_3$), 32.6 (C(**C**$H_3)_3$), 29.9 (CH_2), 28.1 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.3 (CH_2); ν_{max}/cm^{-1} (thin film) 2930, 1646, 1588, 1570, 1488, 1434, 1337, 1214, 1051, 908, 727, 699, 610; HRMS (ESI); calcd. for $C_{29}H_{35}N_2O^+$, 427.2744. Found: $[MH]^+$, 427.2747 (–0.7 ppm error).

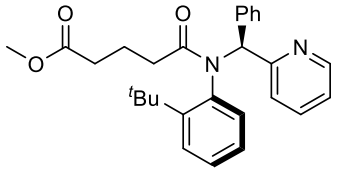
Benzyl 4-((2-(*tert*-butyl)phenyl)(phenyl(pyridin-2-yl)methyl)carbamoyl)piperidine-1-carboxylate (3.116)



To a mixture of 2-(*tert*-butyl)-*N*-(phenyl(pyridin-2-yl)methyl)aniline **3.73** (191 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added benzyl 4-(chlorocarbonyl)piperidine-1-carboxylate (341 mg, 1.21 mmol, prepared from 1-benzyloxycarbonylpiperidine-4-carboxylic acid using the general procedure) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 79:20:1 hexane:ethyl acetate:triethylamine → 69:30:1 hexane:ethyl acetate:triethylamine) to yield the title compound (213 mg, 70%) as a colourless oil. R_f 0.42 (69:30:1 hexane:ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 8.52–8.48 (1H, m, ArH), 7.77 (1H, d, *J* = 8.0 Hz, ArH), 7.50–7.22 (13H, m, ArH), 7.18 (1H, t, *J* = 7.5 Hz, ArH), 7.08–7.02 (1H, m, ArH), 6.80 (1H, d, *J* = 8.0 Hz, ArH), 6.45 (1H, s, NCH), 5.10 (2H, s, $PhCH_2$), 4.27–3.93 (2H, m, NCH_2),

2.72–2.26 (3H, m, NCH_2, COCH), 2.03–1.81 (2H, m, CH_2), 1.75–1.48 (2H, m, CH_2), 1.12 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 175.1 (CO), 158.8 (CO), 155.2 (ArC), 148.5 (ArC), 147.2 (ArC), 140.0 (ArC), 139.4 (ArC), 136.9 (ArC), 135.8 (ArC), 132.0 (ArC), 130.6 (ArC), 129.2 (ArC), 128.5 (2 x ArC), 128.4 (ArC), 127.9 (ArC), 127.8 (ArC), 127.5 (ArC), 126.7 (ArC), 125.4 (ArC), 122.1 (ArC), 71.2 (NCH), 67.0 ($PhCH_2$), 43.5 (NCH_2), 43.0 (NCH_2), 41.0 (CO**C**H), 36.5 (**C**$(CH_3)_3$), 32.6 (C(**C**$H_3)_3$), 28.6 (CH_2), 27.2 (CH_2); ν_{max}/cm^{-1} (thin film) 2956, 1694, 1652, 1588, 1488, 1433, 1339, 1210, 1122, 909, 761, 727, 697, 611; HRMS (ESI); calcd. for $C_{36}H_{40}N_3O_3^+$, 562.3064. Found: $[MH]^+$, 562.3079 (–2.6 ppm error).

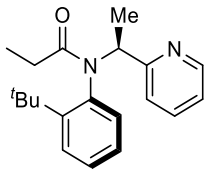
Methyl 5-((2-(*tert*-Butyl)phenyl)(phenyl(pyridin-2-yl)methyl)amino)-5-oxopentanoate (3.117)



To a mixture of 2-(*tert*-butyl)-*N*-(phenyl(pyridin-2-yl)methyl)aniline **3.73** (191 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added methyl 4-(chloroformyl)butyrate (0.170 mL, 199 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (>95:5) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 79:20:1 hexane:ethyl acetate:triethylamine → 69:30:1 hexane:ethyl acetate:triethylamine) to yield the title compound (208 mg, 77%) as a colourless oil. R_f 0.39 (69:30:1 hexane:ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 8.51–8.46 (1H, m, ArH), 7.65 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.48–7.43 (2H, m, ArH), 7.40–7.13 (7H, m, ArH), 7.06–7.00 (1H, m, ArH), 7.68 (1H, d, *J* = 8.0 Hz, ArH), 6.49 (1H, s, NCH), 3.58 (3H, s, OCH_3), 2.32 (2H, t, *J* = 7.5 Hz, CH_2), 2.20–2.05 (2H, m, CH_2), 2.00–1.83 (2H, m, CH_2), 1.10 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 173.7 (CO), 173.1 (CO), 158.8 (ArC), 148.5 (ArC), 147.4 (ArC), 140.2 (ArC), 139.5 (ArC), 135.7 (ArC), 132.2 (ArC), 130.6 (ArC), 129.1 (ArC), 128.4 (ArC), 128.3 (ArC), 127.3 (ArC), 126.8 (ArC), 125.6 (ArC), 122.1 (ArC), 77.1 (NCH), 51.4 (OCH_3), 36.3 (**C**$(CH_3)_3$), 35.4 (CH_2), 33.2

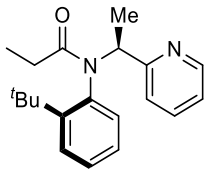
(CH_2), 32.3 (C(**C**H_3)$_3$), 20.3 (CH_2); ν_{max}/cm^{-1} (thin film) 2957, 1734, 1655, 1588, 1570, 1488, 1434, 1386, 1214, 1152, 914, 749, 730, 701, 614; HRMS (ESI); calcd. for $C_{28}H_{32}N_2O_3Na^+$, 467.2305. Found: $[MNa]^+$, 467.2316 (–2.3 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-(pyridin-2-yl)ethyl)propionamide (3.118)**



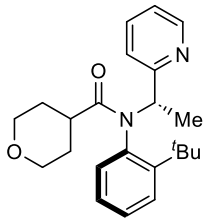
To a mixture of 2-(*tert*-butyl)-*N*-(1-(pyridin-2-yl)ethyl)aniline **3.76** (155 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added propionyl chloride (0.110 mL, 112 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^{1}H NMR spectrum of the crude product was taken to determine the *dr* (85:15) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 7:3 hexane:ethyl acetate) to yield the title compound **3.118** (154 mg, 82%) as a white solid and atropisomer **3.119** (22 mg, 12%) as a colourless oil. Data for **3.118**: R_f 0.10 (8:2 hexane:ethyl acetate); m.p. 76–80 °C; δ_H (400 MHz, $CDCl_3$) 8.42–8.35 (1H, m, ArH), 7.53–7.45 (1H, m, ArH), 7.42–7.46 (1H, m, ArH), 7.29–7.05 (4H, m, ArH), 6.98–6.93 (1H, m, ArH), 5.43 (1H, q, *J* = 7.0 Hz, NCH), 2.05–1.91 (2H, m, CH_2), 1.84 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 1.12 (9H, s, C(CH_3)$_3$), 1.04 (3H, t, *J* = 7.5 Hz, CH_2C**H**$_3$); δ_C (101 MHz, $CDCl_3$) 174.8 (CO), 160.3 (ArC), 148.5 (ArC), 146.8 (ArC), 139.0 (ArC), 136.2 (ArC), 131.9 (ArC), 130.5 (ArC), 128.4 (ArC), 126.6 (ArC), 124.1 (ArC), 122.4 (ArC), 62.3 (NCH), 36.3 (**C**(CH_3)$_3$), 32.1 (C(**C**H_3)$_3$), 30.0 (CH_2), 20.5 (CH**C**H_3), 9.3 (CH_2**C**H_3); ν_{max}/cm^{-1} (thin film) 2968, 1651, 1589, 1570, 1488, 1435, 1382, 1265, 1233, 1081, 1051, 796, 757; HRMS (ESI); calcd. for $C_{20}H_{26}N_2ONa^+$, 333.1937. Found: $[MNa]^+$, 333.1929 (2.5 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-(pyridin-2-yl)ethyl)propionamide (3.119)**



Following the above procedure the title compound **3.119** (22 mg, 12%) was isolated as a minor product, as a colourless oil. R_f 0.20 (8:2 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.59–8.54 (1H, m, ArH), 7.98 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.64 (1H, td, *J* = 7.5, 2.0 Hz, ArH), 7.57 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.44 (1H, d, *J* = 8.0 Hz, ArH), 7.38–7.31 (1H, m, ArH), 7.28–7.22 (1H, m, ArH), 7.15–7.10 (1H, m, ArH), 5.32 (1H, q, *J* = 7.5 Hz, NCH), 2.03–1.84 (2H, m, CH_2), 1.42 (9H, s, $C(CH_3)_3$), 1.13 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), 0.93 (3H, t, *J* = 7.5 Hz, CH_2C**H**$_3$); δ_C (101 MHz, $CDCl_3$) 174.4 (CO), 163.3 (ArC), 149.1 (ArC), 147.5 (ArC), 137.0 (ArC), 136.3 (ArC), 133.8 (ArC), 130.4 (ArC), 128.4 (ArC), 126.6 (ArC), 122.8 (ArC), 121.7 (ArC), 58.4 (NCH), 36.5 (**C**$(CH_3)_3$), 32.8 (C(**C**$H_3)_3$), 29.5 (CH_2), 20.1 (CH**C**H_3), 9.0 (CH_2**C**H_3); ν_{max}/cm^{-1} (thin film) 2968, 1653, 1592, 1570, 1488, 1474, 1435, 1380, 1273, 1241, 1074, 785, 762, 747; HRMS (ESI); calcd. for $C_{20}H_{27}N_2O^+$, 311.2118. Found: $[MH]^+$, 311.2125 (–2.4 ppm error).

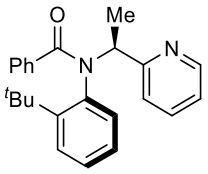
***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-(pyridin-2-yl)ethyl)tetrahydro-2*H*-pyran-4-carboxamide (3.120)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-(pyridin-2-yl)ethyl)aniline **3.76** (155 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added tetrahydro-2*H*-pyran-4-carbonyl chloride (0.150 mL, 180 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^{1}H NMR spectrum of the crude product was taken to determine the *dr* (94:6) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 7:3 hexane:ethyl acetate →

6:4 hexane:ethyl acetate) to yield the title compound (200 mg, 90%) as a white solid. R_f 0.23 (6:4 hexane:ethyl acetate); m.p. 149–151 °C; δ_H (400 MHz, $CDCl_3$) 8.39–8.33 (1H, m, ArH), 7.46 (1H, td, *J* = 8.0, 2.0 Hz, ArH), 7.39 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.27–7.22 (1H, m, ArH), 7.15–6.99 (4H, m, ArH), 5.39 (1H, q, *J* = 7.0 Hz, NCH), 3.95–3.87 (1H, m, OCHH'), 3.82–3.73 (1H, m, OCHH'), 3.18–3.07 (1H, m, OCHH'), 2.98–2.88 (1H, m, OCHH'), 2.22 (1H, tt, *J* = 11.0, 3.5 Hz, COCH), 2.16–2.03 (1H, m, CHH'), 1.80 (3H, d, *J* = 7.0 Hz, CH_3), 1.75–1.62 (1H, m, CHH'), 1.58–1.44 (2H, m, 2 x CHH'), 1.12 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 175.0 (CO), 160.1 (ArC), 148.5 (ArC), 146.8 (ArC), 138.3 (ArC), 136.2 (ArC), 131.8 (ArC), 130.6 (ArC), 128.6 (ArC), 126.3 (ArC), 124.0 (ArC), 122.4 (ArC), 67.2 (OCH_2), 66.9 (OCH_2), 62.2 (NCH), 40.8 (CO**C**H), 36.4 (**C**$(CH_3)_3$), 32.4 (C(**C**$H_3)_3$), 29.8 (CH_2), 28.1 (CH_2), 20.5 (CH**C**H_3); ν_{max}/cm^{-1} (thin film) 2956, 1643, 1591, 1570, 1488, 1435, 1385, 1301, 1240, 1129, 1083, 916, 759, 728, 559; HRMS (ESI); calcd. for $C_{23}H_{31}N_2O_2^+$, 367.2380. Found: $[MH]^+$, 367.2378 (0.5 ppm error).

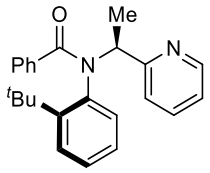
***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-(pyridin-2-yl)ethyl)benzamide (3.121)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-(pyridin-2-yl)ethyl)aniline **3.76** (155 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added benzoyl chloride (0.140 mL, 170 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (91:9) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 7:3 hexane:ethyl acetate) to yield the title compound (157 mg, 72%) as a white solid. R_f 0.16 (8:2 hexane:ethyl acetate); m.p. 129–131 °C; δ_H (400 MHz, $CDCl_3$) 8.43 (1H, d, *J* = 5.0 Hz, ArH), 7.53–7.45 (2H, m, ArH), 7.31–7.23 (3H, m, ArH), 7.19–7.03 (7H, m, ArH), 5.80 (1H, q, *J* = 7.0 Hz, NCH), 2.01 (3H, d, *J* = 7.0 Hz, CH_3), 0.93 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 169.4 (CO), 159.4 (ArC), 148.5 (ArC), 146.8 (ArC), 138.1 (ArC), 137.2 (ArC), 136.0 (ArC), 133.1 (ArC), 131.0 (ArC), 129.5 (ArC),

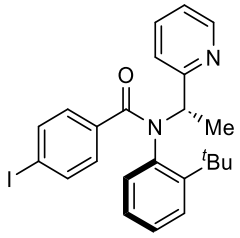
129.2 (ArC), 128.1 (ArC), 127.2 (ArC), 125.6 (ArC), 124.4 (ArC), 122.4 (ArC), 62.8 (NCH), 36.2 (**C**$(CH_3)_3$), 32.1 (C(**C**$H_3)_3$), 20.1 (CH_3); ν_{max}/cm^{-1} (thin film) 2959, 1631, 1567, 1489, 1435, 1369, 1340, 1233, 1051, 760, 717, 697; HRMS (ESI); calcd. for $C_{24}H_{27}N_2O^+$, 359.2118. Found: $[MH]^+$, 359.2111 (1.8 ppm error).

_N_-(2-(_tert_-Butyl)phenyl)-_N_-(1-(pyridin-2-yl)ethyl)benzamide (3.121')



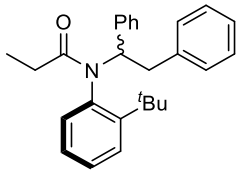
A solution of *N*-(2-(*tert*-butyl)phenyl)-*N*-(1-(pyridin-2-yl)ethyl)benzamide **3.121** (53 mg, 0.148 mmol) in d_6-DMSO (1.0 mL) was heated to 150 °C for 2 h. The reaction mixture was dissolved in DCM (10 mL) and washed with water (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate) to yield the title compound (38 mg, 72%) as a white solid. R_f 0.25 (8:2 hexane:ethyl acetate); m.p. 125–128 °C; δ_H (400 MHz, $CDCl_3$) 8.67–8.62 (1H, m, ArH), 8.40–8.35 (1H, m, ArH), 7.67 (1H, td, *J* = 7.5, 2.0 Hz, ArH), 7.58 (1H, d, *J* = 8.0 Hz, ArH), 7.35–7.22 (5H, m, ArH), 7.18–7.11 (2H, m, ArH), 7.09–7.03 (2H, m, ArH), 5.59 (1H, q, *J* = 7.5 Hz, NCH), 1.28 (3H, d, *J* = 7.5 Hz, CH_3), 1.14 (9H, s, C$(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 169.6 (CO), 162.8 (ArC), 149.3 (ArC), 147.6 (ArC), 136.8 (ArC), 136.5 (ArC), 136.3 (ArC), 134.7 (ArC), 130.7 (ArC), 129.7 (ArC), 129.5 (ArC), 128.2 (ArC), 127.3 (ArC), 125.6 (ArC), 123.2 (ArC), 121.9 (ArC), 59.1 (NCH), 36.3 (**C**$(CH_3)_3$), 32.4 (C(**C**$H_3)_3$), 20.1 (CH**C**H_3); ν_{max}/cm^{-1} (thin film) 2968, 1629, 1594, 1572, 1489, 1435, 1366, 1281, 1243, 1102, 916, 764, 695, 602; HRMS (ESI); calcd. for $C_{24}H_{27}N_2O^+$, 359.2118. Found: $[MH]^+$, 359.2122 (–1.0 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-4-iodo-*N*-(1-(pyridin-2-yl)ethyl)benzamide (3.122)**



To a mixture of 2-(*tert*-butyl)-*N*-(1-(pyridin-2-yl)ethyl)aniline **3.76** (155 mg, 0.605 mmol) and sodium bicarbonate (203 mg, 2.42 mmol) in dry acetonitrile (3 mL) was added 4-iodobenzoyl chloride (322 mg, 1.21 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. At this point, a ^1H NMR spectrum of the crude product was taken to determine the *dr* (92:8) of the reaction before chromatography. The crude product was then purified by column chromatography (SiO_2, 79:20:1 hexane:ethyl acetate:triethylamine) to yield the title compound (270 mg, 92%) as a colourless oil. R_f 0.26 (79:20:1 hexane:ethyl acetate:triethylamine); δ_H (400 MHz, $CDCl_3$) 8.42 (1H, d, *J* = 4.5 Hz, ArH), 7.52–7.40 (4H, m, ArH), 7.25–6.97 (7H, m, ArH), 5.75 (1H, q, *J* = 7.0 Hz, NCH), 1.99 (3H, d, *J* = 7.0 Hz, CH_3), 0.94 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 168.5 (CO), 159.3 (ArC), 148.7 (ArC), 146.9 (ArC), 138.1 (ArC), 136.9 (ArC), 136.5 (ArC), 136.0 (ArC), 133.0 (ArC), 131.3 (ArC), 131.2 (ArC), 128.3 (ArC), 125.9 (ArC), 124.4 (ArC), 122.5 (ArC), 96.0 (ArC), 63.0 (NCH), 36.3 (**C**$(CH_3)_3$), 32.3 ($C(\mathbf{C}H_3)_3$), 20.1 (CH**C**H_3); ν_{max}/cm^{-1} (thin film) 2964, 1627, 1584, 1488, 1435, 1392, 1338, 1006, 909, 835, 748, 727; HRMS (ESI); calcd. for $C_{24}H_{26}IN_2O^+$, 485.1084. Found: $[MH]^+$, 485.1082 (0.4 ppm error).

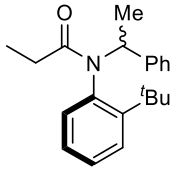
***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1,2-diphenylethyl)propionamide (3.85a)**



To a mixture of 2-(*tert*-butyl)-*N*-(1,2-diphenylethyl)aniline **3.77** (100 mg, 0.303 mmol) and sodium bicarbonate (102 mg, 1.12 mmol) in dry acetonitrile (1.5 mL) was added propionyl chloride (0.050 mL, 56 mg, 0.606 mmol) and the resulting mixture was heated to 80 °C for

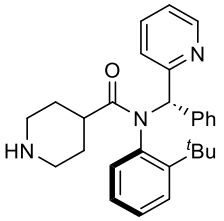
1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 9:1 hexane:ethyl acetate) to yield the title compound (22 mg, 19%) as a colourless oil and a 3:1 mixture of diastereoisomers. R_f 0.29 (9:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.63 (1H, dd, *J* = 8.0, 1.5 Hz, ArH, major diastereoisomer), 7.42–7.27 (6H, m, ArH, both diastereoisomers), 7.26–7.02 (15H, m, ArH, both diastereoisomers), 7.00–6.94 (2H, m, ArH), 6.92–6.86 (2H, m, ArH), 6.70–6.65 (2H, m, ArH), 5.62 (1H, dd, *J* = 11.5, 3.0 Hz, NCH, minor diastereoisomer), 5.36 (1H, dd, *J* = 12.0, 4.0 Hz, NCH, major diastereoisomer), 3.58 (1H, dd, *J* = 12.0, 3.0 Hz, ArC**H**H', minor diastereoisomer), 3.32 (1H, dd, *J* = 12.0, 11.5 Hz, ArCH**H'**, minor diastereoisomer), 3.18 (1H, dd, *J* = 13.5, 4.0 Hz, ArC**H**H', major diastereoisomer), 2.63 (1H, dd, *J* = 13.5, 12.0 Hz, ArCH**H'**, major diastereoisomer), 2.09 (2H, q, *J* = 7.5 Hz, $COCH_2$, minor diastereoisomer), 2.04–1.81 (2H, m, $COCH_2$, major diastereoisomer), 1.45 (9H, s, $C(CH_3)_3$, major diastereoisomer), 1.14 (3H, t, *J* = 7.5 Hz, CH_3, minor diastereoisomer), 0.98 (3H, t, *J* = 7.5 Hz, CH_3, major diastereoisomer), 0.91 (9H, s, $C(CH_3)_3$, minor diastereoisomer); δ_C (101 MHz, $CDCl_3$) 174.1 (CO, minor diastereoisomer), 174.0 (CO, major diastereoisomer), 147.9 (ArC), 147.7 (ArC), 140.9 (ArC), 138.4 (ArC), 138.1 (ArC), 138.0 (ArC), 137.5 (ArC), 137.0 (ArC), 132.2 (ArC), 131.7 (ArC), 131.2 (2 x ArC), 131.1 (ArC), 129.4 (ArC), 129.3 (ArC), 129.2 (ArC), 128.6 (ArC), 128.5 (ArC), 128.1 (ArC), 128.0 (ArC), 127.9 (ArC), 127.7 (2 x ArC), 127.1 (ArC), 126.8 (ArC), 126.6 (ArC), 126.2 (ArC), 126.0 (ArC), 65.6 (NCH, minor diastereoisomer), 64.6 (NCH, major diastereoisomer), 42.7 ($ArCH_2$, minor diastereoisomer), 39.8 ($ArCH_2$, major diastereoisomer), 36.7 (**C**$(CH_3)_3$, major diastereoisomer), 36.4 (**C**$(CH_3)_3$, minor diastereoisomer), 32.9 (C(**C**$H_3)_3$, major diastereoisomer), 32.1 (C(**C**$H_3)_3$, minor diastereoisomer), 30.0 (CO**C**H_2, minor diastereoisomer), 29.9 (CO**C**H_2, major diastereoisomer), 9.3 (CH_3, minor diastereoisomer), 9.0 (CH_3, major diastereoisomer); ν_{max}/cm^{-1} (thin film) 2971, 1651, 1487, 1436, 1378, 1261, 1079, 1051, 909, 760, 729, 697, 645, 543; HRMS (ESI); calcd. for $C_{27}H_{32}NO^+$, 386.2478. Found: $[MH]^+$, 386.2480 (–0.4 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-*N*-(1-phenylethyl)propionamide (3.146a)**



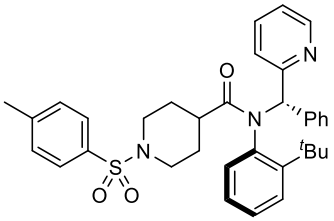
To a mixture of 2-(*ter*t-butyl)-*N*-(1-phenylethyl)aniline **3.78** (100 mg, 0.395 mmol) and sodium bicarbonate (133 mg, 1.58 mmol) in dry acetonitrile (2 mL) was added propionyl chloride (0.070 mL, 73 mg, 0.790 mmol) and the resulting mixture was heated to 80 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, 9:1 hexane:ethyl acetate) to yield the title compound (76 mg, 62%) as a 2:1 mixture of diastereoisomers and as a colourless oil. R_f 0.23 (9:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.61 (1H, dd, *J* = 8.0, 1.5 Hz, ArH, major diastereoisomer), 7.49–7.45 (2H, m, ArH), 7.39–7.19 (7H, m, ArH), 7.16–7.01 (4H, m, ArH), 6.92–6.85 (4H, m, ArH), 5.66–5.85 (2H, m, NCH, both diastereoisomers), 2.06–1.82 (4H, m, $COCH_2$, both diastereoisomers), 1.70 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$, minor diastereoisomer), 1.42 (9H, s, $C(CH_3)_3$, major diastereoisomer), 1.21 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$, major diastereoisomer), 1.08 (3H, t, *J* = 7.5 Hz, CH_2C**H**$_3$, minor diastereoisomer), 0.99 (3H, t, *J* = 7.5 Hz, CH_2C**H**$_3$, major diastereoisomer), 0.93 (9H, s, $C(CH_3)_3$, minor diastereoisomer); δ_C (101 MHz, $CDCl_3$) 174.2 (CO, major diastereoisomer), 174.1 (CO, minor diastereoisomer), 147.8 (ArC), 147.7 (ArC), 143.9 (ArC), 140.0 (ArC), 137.5 (ArC), 136.6 (ArC), 132.2 (ArC), 131.9 (ArC), 131.2 (ArC), 131.0 (ArC), 130.2 (ArC), 128.4 (2 x ArC), 128.2 (ArC), 218.0 (ArC), 127.7 (2 x ArC), 127.0 (ArC), 126.4 (2 x ArC), 58.6 (NCH, minor diastereoisomer), 55.3 (NCH, major diastereoisomer), 36.7 (**C**$(CH_3)_3$, major diastereoisomer), 36.4 (**C**$(CH_3)_3$, minor diastereoisomer), 32.9 (C(**C**$H_3)_3$, major diastereoisomer), 32.1 (C(**C**$H_3)_3$, minor diastereoisomer), 30.0 (CO**C**H_2, minor diastereoisomer), 29.9 (CO**C**H_2, major diastereoisomer), 22.0 (CH**C**H_3, minor diastereoisomer), 19.5 (CH**C**H_3, major diastereoisomer), 9.4 (CH_2**C**H_3, minor diastereoisomer), 9.1 (CH_2**C**H_3, major diastereoisomer); ν_{max}/cm^{-1} (thin film) 2972, 1652, 1487, 1436, 1381, 1266, 1231, 1052, 918, 760, 733, 699; HRMS (ESI); calcd. for $C_{21}H_{28}NO^+$, 310.2165. Found: $[MH]^+$, 310.2158 (2.2 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-*N*-(phenyl(pyridin-2-yl)methyl)piperidine-4-carboxamide (3.151)**



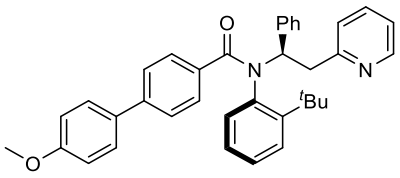
To a solution of benzyl 4-((2-(*tert*-butyl)phenyl)(phenyl(pyridin-2-yl)methyl)carbamoyl)piperidine-1-carboxylate **3.116** (82 mg, 0.146 mmol) in dry degassed methanol (1.0 mL) was added 10% palladium on carbon (8 mg). The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 18 h. The suspension was filtered through Celite and the filtrate concentrated *in vacuo* to yield the title compound (42 mg, 67%) as a white solid. m.p. 99–103 °C; δ_H (400 MHz, $CDCl_3$) 9.19 (1H, br s, NH), 8.50–8.44 (1H, m, ArH), 7.94–7.86 (1H, m, ArH), 7.51–7.40 (4H, m, ArH), 7.37–7.17 (5H, m, ArH), 7.07 (1H, dd, *J* = 7.5, 5.0 Hz, ArH), 6.78 (1H, d, *J* = 8.0 Hz, ArH), 6.12 (1H, s, NCH), 3.65–3.51 (1H, m, NC**H**H'), 3.19–3.08 (1H, m, NC**H**H'), 2.89–2.72 (2H, m, 2 x NCH**H'**), 2.50–2.37 (1H, m, CHCO), 2.12–1.75 (4H, m, CHH'), 1.06 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 174.3 (CO), 158.7 (ArC), 148.5 (ArC), 146.9 (ArC), 140.3 (ArC), 139.3 (ArC), 136.1 (ArC), 131.5 (ArC), 130.6 (ArC), 129.9 (ArC), 128.7 (ArC), 128.6 (ArC), 127.9 (ArC), 127.2 (ArC), 124.5 (ArC), 122.2 (ArC), 72.9 (NCH), 41.9 (NCH_2), 41.8 (NCH_2), 36.4 (**C**HCO), 36.3 (**C**$(CH_3)_3$), 32.6 (C(**C**$H_3)_3$), 24.6 (CH_2), 24.0 (CH_2); v_{max}/cm^{-1} (thin film) 3401, 2958, 2803, 2494, 1651, 1588, 1488, 1469, 1434, 1389, 1230, 1093, 891, 760, 730, 701; HRMS (ESI); calcd. for $C_{28}H_{34}N_3O^+$, 428.2696. Found: $[MH]^+$, 428.2698 (–0.3 ppm error).

_N_-(2-(_tert_-Butyl)phenyl)-_N_-(phenyl(pyridin-2-yl)methyl)-1-tosylpiperidine-4-carboxamide (3.152)



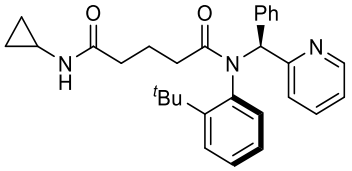
To a solution of *N*-(2-(*tert*-butyl)phenyl)-*N*-(phenyl(pyridin-2-yl)methyl)piperidine-4-carboxamide **3.151** (42 mg, 0.0982 mmol) in DCM (1.0 mL) was added triethylamine (0.040 mL, 30 mg, 0.294 mmol) followed by *p*-toluenesulfonyl chloride (37 mg, 0.196 mmol) and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 8:2 hexane:ethyl acetate → 7:3 hexane:ethyl acetate) to yield the title compound (56 mg, 98%) as a white solid. R_f 0.33 (7:3 hexane:ethyl acetate); m.p. 114–118 °C; δ_H (400 MHz, $CDCl_3$) 8.50–8.45 (1H, m, ArH), 7.76 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.57 (2H, d, *J* = 8.0 Hz, ArH), 7.46–7.12 (12H, m, ArH, 7.06 (1H, dd, *J* = 7.5, 4.5 Hz, ArH), 6.78 (1H, d, *J* = 8.0 Hz, ArH), 6.33 (1H, s, NCH), 3.79–3.73 (1H, m, NC**H**H'), 3.66–3.59 (1H, m, NC**H**H'), 2.40 (3H, s, $ArCH_3$), 2.17–2.05 (3H, m, NCH**H'**, CHCO, C**H**H'), 2.01–1.89 (2H, m, NCH**H'**, C**H**H'), 1.77–1.64 (2H, m, 2 x CH**H'**), 1.04 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 174.7 (CO), 158.8 (ArC), 148.5 (ArC), 147.3 (ArC), 143.5 (ArC), 139.8 (ArC), 139.7 (ArC), 135.9 (ArC), 133.8 (ArC), 132.0 (ArC), 130.5 (ArC), 129.7 (ArC), 129.4 (ArC), 128.6 (ArC), 128.3 (ArC), 127.7 (ArC), 127.6 (ArC), 126.8 (ArC), 125.2 (ArC), 122.1 (ArC), 71.7 (NCH), 45.5 (NCH_2), 45.0 (NCH_2), 40.2 (**C**HCO), 36.4 (**C**$(CH_3)_3$), 32.6 (C(**C**$H_3)_3$), 28.3 (CH_2), 27.0 (CH_2), 21.6 ($ArCH_3$); v_{max}/cm^{-1} (thin film) 2959, 1651, 1588, 1488, 1434, 1340, 1222, 1162, 1053, 931, 909, 723, 701; HRMS (ESI); calcd. for $C_{35}H_{40}N_3O_3S^+$, 582.2785. Found: $[MH]^+$, 582.2784 (0.2 ppm error).

_N_-(2-(_tert_-Butyl)phenyl)-4'-methoxy-_N_-(1-phenyl-2-(pyridin-2-yl)ethyl)-[1,1'-biphenyl]-4-carboxamide (3.154)



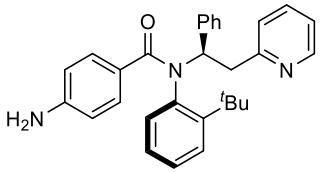
To a solution of 4-bromo-*N*-(2-(*tert*-butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide **3.104** (63 mg, 0.123 mmol) in degassed 1,2-dimethoxyethane (1.0 mL) was added caesium carbonate (0.200 mL, 2.1 M in water, 0.431 mmol), 4-methoxyphenylboronic acid (28 mg, 0.185 mmol) and tetrakis(triphenylphosphine)palladium (7 mg, 6.15 µmol) and the reaction mixture was heated to 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* and redissolved in ethyl acetate (10 mL). This was washed with water (10 mL) and brine (10 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 7:3 hexane:ethyl acetate) to yield the title compound (43 mg, 65%) as a white solid. R_f 0.24 (7:3 hexane:ethyl acetate); m.p. 42–44 °C; δ_H (400 MHz, $CDCl_3$) 8.56–8.52 (1H, m, ArH), 7.63–7.58 (2H, m, ArH), 7.46–7.34 (5H, m, ArH), 7.31–7.19 (9H, m, ArH), 7.06 (1H, dd, *J* = 7.5, 5.0 Hz, ArH), 6.98 (1H, d, *J* = 8.0 Hz, ArH), 6.94–6.88 (2H, m, ArH), 6.00 (1H, dd, *J* = 11.0, 5.0 Hz, CH), 3.81 (3H, s, OCH_3), 3.58 (1H, dd, *J* = 13.5, 5.0 Hz, C**H**H'), 3.18 (1H, dd, *J* = 13.5, 11.0 Hz, CH**H'**), 1.09 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 169.6 (CO), 159.6 (ArC), 158.5 (ArC), 149.4 (ArC), 147.9 (ArC), 141.7 (ArC), 140.6 (ArC), 138.5 (ArC), 136.2 (ArC), 135.2 (ArC), 132.5 (ArC), 132.4 (ArC), 131.6 (ArC), 130.4 (ArC), 129.2 (ArC), 128.2 (3 x ArC), 127.5 (ArC), 126.2 (ArC), 125.3 (ArC), 124.3 (ArC), 121.6 (ArC), 114.3 (ArC), 64.9 (CH), 55.4 (OCH_3), 42.0 (CH_2), 36.5 (**C**$(CH_3)_3$), 32.5 (C(**C**$H_3)_3$); ν_{max}/cm^{-1} (thin film) 2959, 1631, 1605, 1490, 1436, 1357, 1293, 1247, 1039, 909, 766, 729, 699; HRMS (ESI); calcd. for $C_{37}H_{37}N_2O_2^+$, 541.2850. Found: $[MH]^+$, 541.2831 (3.4 ppm error).

N^1-(2-(*tert*-Butyl)phenyl)-N^5-cyclopropyl-N^1-(phenyl(pyridin-2-yl)methyl)glutaramide (3.157)



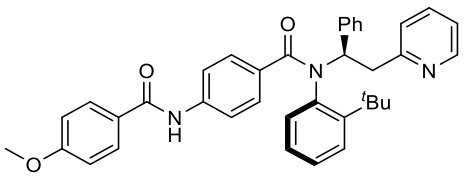
To a solution of methyl 5-((2-(*tert*-Butyl)phenyl)(phenyl(pyridin-2-yl)methyl)amino)-5-oxopentanoate **3.117** (64 mg, 0.144 mmol) in THF (0.50 mL) was added lithium hydroxide (0.320 mL, 0.5 M in water, 0.158 mmol) and the mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and chloroform was added and removed *in vacuo* three times to form an azeotropic mixture and remove traces of water ahead of the next step. The intermediate lithium salt was dissolved in chloroform (1.4 mL) and to this was added DIPEA (0.130 mL, 93 mg, 0.720 mmol), T3P (0.080 mL, 50% in ethyl acetate, 0.216 mmol) and cyclopropylamine (0.020 mL, 12 mg, 0.216 mmol) and the reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 8:2 ethyl acetate:hexane → ethyl acetate) to yield the title compound (60 mg, 89%) as a yellow oil. R_f 0.49 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.50–8.44 (1H, m, ArH), 7.67 (1H, dd, *J* = 8.0, 2.0 Hz, ArH), 7.48–7.15 (9H, m, ArH), 7.07 (1H, dd, *J* = 7.5, 5.0 Hz, ArH), 6.77 (1H, d, *J* = 8.0 Hz, ArH), 6.49 (1H, br s, NH), 6.39 (1H, s, NCH), 2.67–2.59 (1H, m, C**H**CH_2), 2.22–2.02 (4H, m, 2 x $COCH_2$), 1.95–1.77 (2H, m, CH_2), 1.07 (9H, s, $C(CH_3)_3$), 0.75–0.67 (2H, m, CHC**H**$_2$), 0.47–0.39 (2H, m, CHC**H**$_2$); δ_C (101 MHz, $CDCl_3$) 174.6 (CO), 173.5 (CO), 158.9 (ArC), 148.4 (ArC), 147.4 (ArC), 139.9 (ArC), 139.6 (ArC), 136.0 (ArC), 131.9 (ArC), 130.9 (ArC), 129.3 (ArC), 128.5 (ArC), 128.4 (ArC), 127.6 (ArC), 127.0 (ArC), 125.5 (ArC), 122.2 (ArC), 71.8 (NCH), 36.4 (**C**$(CH_3)_3$), 35.6 (CO**C**H_2), 35.0 (CO**C**H_2), 32.4 (C(**C**$H_3)_3$), 22.6 (**C**HCH_2), 21.4 (CH_2), 6.6 (CH**C**H_2), 6.3 (CH**C**H_2); ν_{max}/cm^{-1} (thin film) 3297, 2961, 1644, 1589, 1488, 1434, 1389, 1248, 909, 729, 700, 614; HRMS (ESI); calcd. for $C_{30}H_{36}N_3O_2^+$, 470.2802. Found: $[MH]^+$, 470.2815 (–2.7 ppm error).

4-Amino-*N*-(2-(*tert*-butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide (3.158)



To a solution of *N*-(2-(*tert*-butyl)phenyl)-4-nitro-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide **3.109** (67 mg, 0.140 mmol) in ethanol (0.40 mL) and water (0.40 mL) was added ammonium chloride (37 mg, 0.700 mmol) and iron powder (39 mg, 0.700 mmol) and the mixture was stirred at room temperature for 24 h. The solids were filtered off and washed with DCM and MeOH and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 1:1 hexane:ethyl acetate) to yield the title compound (42 mg, 67%) as an orange solid. R_f 0.23 (1:1 hexane:ethyl acetate). m.p. 61–65 °C; δ_H (400 MHz, $CDCl_3$) 8.54–8.45 (1H, m, ArH), 7.60–6.91 (15H, m, ArH), 6.29 (1H, d, *J* = 8.5 Hz, ArH), 5.98–5.87 (1H, m, CH), 4.32 (2H, br s, NH_2), 3.58–3.46 (1H, m, C**H**H'), 3.25–3.12 (1H, m, CH**H'**), 1.07 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 169.7 (CO), 158.5 (ArC), 149.2 (ArC), 147.8 (ArC), 140.8 (ArC), 138.9 (ArC), 136.3 (ArC), 132.4 (ArC), 131.8 (ArC), 131.5 (ArC), 130.9 (ArC), 129.0 (ArC), 128.1 (ArC), 127.9 (ArC), 127.3 (ArC), 126.1 (ArC), 124.3 (ArC), 121.6 (ArC), 113.3 (ArC), 111.1 (ArC), 64.7 (CH), 42.0 (CH_2), 36.5 (**C**$(CH_3)_3$), 32.4 (C(**C**$H_3)_3$); v_{max}/cm^{-1} (thin film) 3343, 2959, 1692, 1598, 1435, 1358, 1303, 1239, 1183, 1145, 909, 764, 729, 699; HRMS (ESI); calcd. for $C_{30}H_{32}N_3O^+$, 450.2540. Found: $[MH]^+$, 450.2538 (0.4 ppm error).

***N*-(2-(*tert*-Butyl)phenyl)-4-(4-methoxybenzamido)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide (3.160)**



To a solution of 4-amino-*N*-(2-(*tert*-butyl)phenyl)-*N*-(1-phenyl-2-(pyridin-2-yl)ethyl)benzamide **3.158** (40 mg, 0.0890 mmol) in DCM (0.90 mL) was added triethylamine (0.030 mL, 18 mg, 0.178 mmol) followed by 4-methoxybenzoyl chloride (18 mg, 0.107 mmol) and the mixture was stirred at room temperature for 18 h. The reaction was

quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 1:1 ethyl acetate:hexane → 7:3 ethyl acetate:hexane) to yield the title compound (16 mg, 31%) as a yellow oil. R_f 0.30 (1:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.56–8.50 (1H, m, ArH), 7.79–7.73 (2H, m, ArH), 7.60–7.54 (2H, m, ArH), 7.44–7.34 (5H, m, ArH), 7.29–7.17 (8H, m, ArH), 7.07–7.02 (1H, m, ArH), 6.96–6.90 (3H, m, ArH), 5.97 (1H, dd, *J* = 11.0, 5.0 Hz, CH), 3.85 (3H, s, OCH_3), 3.53 (1H, dd, *J* = 13.5, 5.0 Hz, C**H**H'), 3.14 (1H, dd, *J* = 13.5, 11.0 Hz, CH**H'**), 1.09 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 169.2 (CO), 165.1 (CO), 162.7 (ArC), 158.5 (ArC), 149.5 (ArC), 147.9 (ArC), 140.7 (ArC), 139.4 (ArC), 138.5 (ArC), 136.2 (ArC), 132.6 (ArC), 132.4 (ArC), 131.7 (ArC), 131.1 (ArC), 129.2 (ArC), 129.0 (ArC), 128.3 (ArC), 128.2 (ArC), 127.5 (ArC), 126.9 (ArC), 126.3 (ArC), 124.3 (ArC), 121.6 (ArC), 118.1 (ArC), 114.1 (ArC), 65.0 (CH), 55.6 (OCH_3), 42.1 (CH_2), 36.5 (**C**$(CH_3)_3$), 32.6 ($C(\mathbf{C}H_3)_3$); ν_{max}/cm^{-1} (thin film) 3310, 2923, 1731, 1599, 1512, 1361, 1308, 1247, 1177, 1029, 907, 763, 729, 699; HRMS (ESI); calcd. for $C_{38}H_{38}N_3O_3^+$, 584.2908. Found: $[MH]^+$, 584.2927 (–3.2 ppm error).

4.3 Computational Chemistry

The structures were loaded in PCModel,[128] and a conformational analysis was performed using the Molecular Mechanics Force Field (MMFF94) level of theory.[129–133] The structures within 3.5 kcal mol^{-1} of the lowest energy conformation were kept and the geometry of each structure was optimised using the Gaussian 16, Revision C.02 package,[134] at the B3LYP/6-31G* level of theory.[135–139] The lowest energy structure was then reoptimised with tight convergence criteria followed by frequency calculations, which confirmed the structures were minima due to the absence of imaginary frequencies.

For the methodology screening, single point calculations were carried out on the B3LYP/6-31G* optimised structures using the stated functional (B3LYP, M06-2X[140] or PBE0[141,142]) and basis set (6-31G* or def2-TZVPP[143–146]). All minima were again confirmed as such by the absence of imaginary frequencies. The SCF energies were corrected for their zero-point energies, thermal energies and entropies are at 298 K unless stated otherwise, obtained from the frequency calculations. Optimisations were performed with tight convergence criteria and no symmetry constraints were applied. An ultrafine integral grid was used for all calculations. Where used, solvent corrections were applied with the SMD model.[147] Where used, dispersion effects were modelled with Grimme's D3 method with additional Becke–Johnson damping.[148]

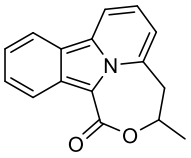
Transition states were located by performing a scan of the bond length of the relevant bond being formed/broken. The highest energy structures from the scans were retained and optimised to a transition state using the Berny algorithm[149] at the B3LYP/6-31G* level of theory. This was followed by a frequency calculation to confirm there was a single imaginary frequency. Intrinsic Reaction Coordinate (IRC) analysis[150–152] confirmed that the transition states were connected to the appropriate minima.

Energies and xyz coordinates are published in *Chemical Science*.[114]

4.4 X-ray Crystallography Data

Crystals were obtained by dissolving a sample in hexane with minimal amounts of DCM to ensure full dissolution. Samples were left in a loosely closed sample vial to allow the slow evaporation of solvent until crystals were formed. All crystallographic data were deposited with the Cambridge Crystallographic Data Centre (CCDC).

X-ray crystallographic data and structure refinement for compound **2.69a**, wpu23003.



2.69a
CCDC: 2267185

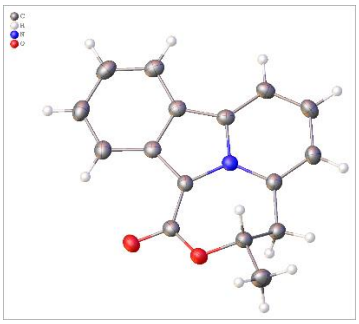
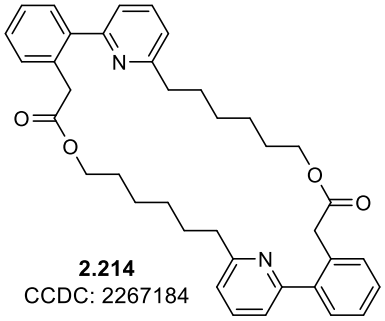


Table 1 Crystal data and structure refinement for wpu23003.

Identification code	wpu23003
Empirical formula	$C_{16}H_{13}NO_2$
Formula weight	251.27
Temperature/K	111(2)
Crystal system	orthorhombic
Space group	Pbca
a/Å	13.5015(2)
b/Å	7.30430(10)
c/Å	24.5454(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2420.64(6)
Z	8
ρ_{calc}g/cm^3	1.379
μ/mm^{-1}	0.736
F(000)	1056.0
Crystal size/mm^3	0.26 × 0.19 × 0.07
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.202 to 153.71
Index ranges	-16 ≤ h ≤ 17, -8 ≤ k ≤ 3, -30 ≤ l ≤ 25
Reflections collected	8134
Independent reflections	2452 [R_{int} = 0.0299, R_{sigma} = 0.0330]
Data/restraints/parameters	2452/0/173
Goodness-of-fit on F^2	1.040
Final R indexes [I>=2σ (I)]	R_1 = 0.0360, wR_2 = 0.0924
Final R indexes [all data]	R_1 = 0.0403, wR_2 = 0.0962
Largest diff. peak/hole / e Å^{-3}	0.18/-0.21

X-ray crystallographic data and structure refinement for compound **2.214**, wpu23001a.



2.214
CCDC: 2267184

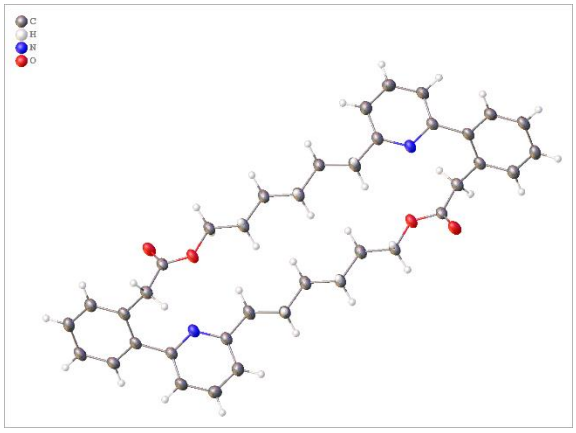
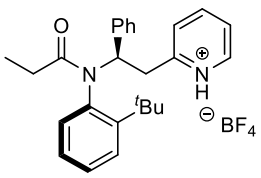


Table 1 Crystal data and structure refinement for wpu23001a.

Identification code	wpu23001a
Empirical formula	$C_{38}H_{42}N_2O_4$
Formula weight	590.73
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	I2/a
a/Å	33.7615(7)
b/Å	4.50570(10)
c/Å	20.5901(4)
α/°	90
β/°	94.572(2)
γ/°	90
Volume/Å^3	3122.18(11)
Z	4
ρ_{calc}g/cm^3	1.257
μ/mm^{-1}	0.641
F(000)	1264.0
Crystal size/mm^3	0.29 × 0.14 × 0.08
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.616 to 153.744
Index ranges	-42 ≤ h ≤ 42, -5 ≤ k ≤ 5, -26 ≤ l ≤ 18
Reflections collected	9768
Independent reflections	3172 [R_{int} = 0.0349, R_{sigma} = 0.0417]
Data/restraints/parameters	3172/0/199
Goodness-of-fit on F^2	1.026
Final R indexes [I>=2σ (I)]	R_1 = 0.0419, wR_2 = 0.1083
Final R indexes [all data]	R_1 = 0.0532, wR_2 = 0.1195
Largest diff. peak/hole / e Å^{-3}	0.21/-0.23

X-ray crystallographic data and structure refinement for compound **3.81**, wpu23012.



3.81
CCDC: 2420889

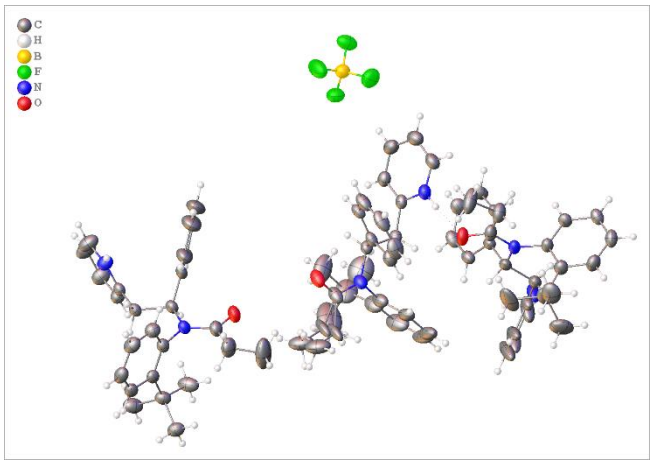
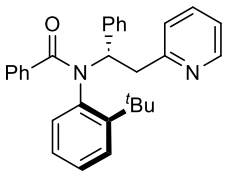


Table 1 Crystal data and structure refinement for wpu23012.

Identification code	wpu23012
Empirical formula	$C_{26}H_{31}B_{0.33}F_{1.33}N_2O$
Formula weight	416.45
Temperature/K	96(20)
Crystal system	triclinic
Space group	P-1
a/Å	11.8452(2)
b/Å	16.8977(3)
c/Å	20.3145(3)
α/°	76.7340(10)
β/°	84.3390(10)
γ/°	84.724(2)
Volume/Å^3	3928.18(11)
Z	6
ρ_{calc}g/cm^3	1.056
μ/mm^{-1}	0.563
F(000)	1336.0
Crystal size/mm^3	0.23 × 0.05 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.52 to 153.95
Index ranges	-14 ≤ h ≤ 14, -21 ≤ k ≤ 19, -18 ≤ l ≤ 25
Reflections collected	44023
Independent reflections	15833 [R_{int} = 0.0381, R_{sigma} = 0.0415]
Data/restraints/parameters	15833/2/854
Goodness-of-fit on F^2	1.027
Final R indexes [I>=2σ (I)]	R_1 = 0.0718, wR_2 = 0.1748
Final R indexes [all data]	R_1 = 0.0915, wR_2 = 0.1859
Largest diff. peak/hole / e Å^{-3}	0.46/-0.32

X-ray crystallographic data and structure refinement for compound **3.98**, wpu23015.



3.98
CCDC: 2363259

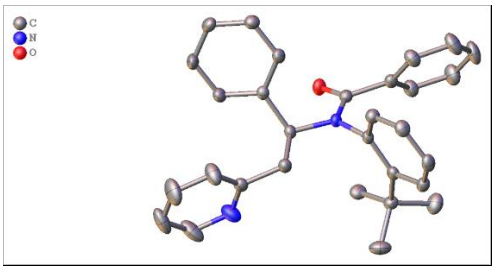
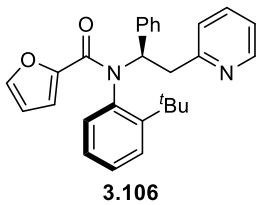


Table 1 Crystal data and structure refinement for wpu23015.

Identification code	wpu23015
Empirical formula	$C_{30}H_{30}N_2O$
Formula weight	434.56
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.85289(15)
b/Å	23.3855(3)
c/Å	8.96547(10)
α/°	90
β/°	104.1645(12)
γ/°	90
Volume/Å^3	2409.55(5)
Z	4
ρ_{calc}g/cm^3	1.198
μ/mm^{-1}	0.559
F(000)	928.0
Crystal size/mm^3	0.272 × 0.19 × 0.143
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.56 to 134.156
Index ranges	$-14 \le h \le 13$, $-27 \le k \le 25$, $-10 \le l \le 10$
Reflections collected	22033
Independent reflections	4305 [R_{int} = 0.0284, R_{sigma} = 0.0191]
Data/restraints/parameters	4305/0/419
Goodness-of-fit on F^2	1.036
Final R indexes [I>=2σ (I)]	R_1 = 0.0349, wR_2 = 0.0890
Final R indexes [all data]	R_1 = 0.0379, wR_2 = 0.0912
Largest diff. peak/hole / e Å^{-3}	0.30/-0.27

X-ray crystallographic data and structure refinement for compound **3.106**, wpu23016.



3.106
CCDC: 2363258

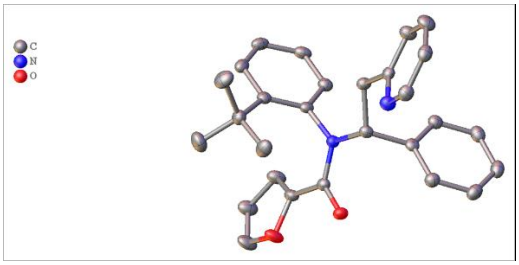
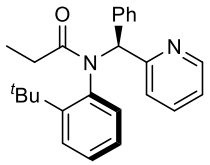


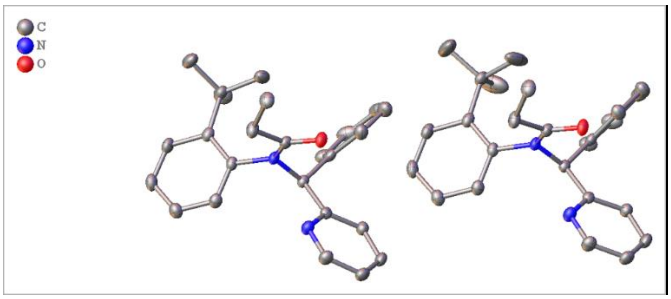
Table 1 Crystal data and structure refinement for wpu23016.

Identification code	wpu23016
Empirical formula	$C_{28}H_{28}N_2O_2$
Formula weight	424.52
Temperature/K	110.2(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.3156(3)
b/Å	15.8552(5)
c/Å	17.6204(6)
α/°	90
β/°	101.442(3)
γ/°	90
Volume/Å^3	2277.00(13)
Z	4
ρ_{calc}g/cm^3	1.238
μ/mm^{-1}	0.613
F(000)	904.0
Crystal size/mm^3	0.161 × 0.059 × 0.049
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.57 to 134.094
Index ranges	$-8 \le h \le 9$, $-18 \le k \le 18$, $-18 \le l \le 21$
Reflections collected	13841
Independent reflections	4055 [R_{int} = 0.0297, R_{sigma} = 0.0290]
Data/restraints/parameters	4055/0/402
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0312, wR_2 = 0.0792
Final R indexes [all data]	R_1 = 0.0365, wR_2 = 0.0819
Largest diff. peak/hole / e Å^{-3}	0.21/-0.14

X-ray crystallographic data and structure refinement for compound **3.112**, wpu24011.



3.112
CCDC: 2363260



Refinement Special Details

The asymmetric unit contained 2 molecules. These are almost related by a half-cell translation parallel to the c-axis. Use of a cell with a c-axis of half the length gave a poorer fit both in terms of R factors and the ADP shape (prolate) as well as having a significant number of reflections with l=0.5.

Table 1 Crystal data and structure refinement for wpu24011.

Identification code	wpu24011
Empirical formula	$C_{25}H_{28}N_2O$
Formula weight	372.49
Temperature/K	109.95(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.02470(10)
b/Å	13.2322(2)
c/Å	18.6064(3)
α/°	100.7280(10)
β/°	100.9090(10)
γ/°	105.8830(10)
Volume/Å^3	2030.78(5)
Z	4
ρ_{calc}g/cm^3	1.218
μ/mm^{-1}	0.574
F(000)	800.0
Crystal size/mm^3	0.23 × 0.19 × 0.12
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.178 to 136.474
Index ranges	$-10 \le h \le 10$, $-15 \le k \le 13$, $-22 \le l \le 17$
Reflections collected	21553
Independent reflections	7416 [R_{int} = 0.0224, R_{sigma} = 0.0261]
Data/restraints/parameters	7416/0/514
Goodness-of-fit on F^2	1.079
Final R indexes [I>=2σ (I)]	R_1 = 0.0393, wR_2 = 0.1064
Final R indexes [all data]	R_1 = 0.0442, wR_2 = 0.1103
Largest diff. peak/hole / e Å^{-3}	0.28/-0.26

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